CRITICAL STUDIES IN NEUROLOGY

Critical Studies in Neurology

BY

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"*Whether or not it is true that the age of adventure in the physical world is now closed, adventure in the world of thought is still open to every soul that is not wholly tamed and in love with the cage. It has always been more difficult than adventure in the ordinary sense, and it is becoming more difficult every day. Uniformity of thought is increasingly the apparent goal and demand of civilization; education has no use for the fires of rebellion, and even science itself is not above lending an occasional hand at the fire engine. Still, there burns on in most of us a small wild spark. I advise you to cherish it as a precious possession. Do not, however, be under any misapprehension. Really to think for oneself is as strange, difficult, and dangerous as any adventure, and, as the wise ones say, 'it will do you no good'; but, like virtue—which it does not otherwise greatly resemble—it will be its own reward.*"—WILFRED TROTTER, "Art and Science in Medicine," from the Collected Papers of Wilfred Trotter, F.R.S., Oxford University Press, 1941.

"*Preserve your originality. It is this which will give your scientific work its frankness, its grace, its elegance, its warmth and life among so many artificial, banal, commonplace, cold and corpse-like works. . . .*" MAURICE ARTHUS, "Philosophy of Scientific Investigation." Translated from the French by Henry Sigerist. Johns Hopkins Press, 1943.

PREFACE

FOR permission to reprint the papers which were originally contributed to *Brain*, my thanks are due to Messrs Macmillan & Co., the publishers of that journal, and, similarly, for permission to reprint "The Integration of Medicine" I have to thank the editor of the *British Medical Journal*.

Dr Conel and the Harvard University Press have kindly allowed me to reproduce Figs. 8 and 10 from the former's monograph on "The Postnatal Development of the Human Cerebral Cortex," Vol. II., while by an arrangement with the Cambridge University Press it has been made possible to reproduce Fig. 9 from A. W. Campbell's "Histological Studies on the Localisation of Cerebral Function."

To Mr Charles Macmillan of Messrs E. & S. Livingstone, as always, I owe the most generous and helpful collaboration. To work with him is a rare pleasure.

F. M. R. WALSHE.

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FOREWORD

FOREWORD

The Function of Criticism in Medicine

THE reprinting of the papers herein collected from the pages of *Brain* was originally planned to meet a continued demand for reprints of the earlier members of the series after these had been exhausted. It has, however, been suggested to me that this republication may serve a wider, if still a modest, purpose : namely, the presentation of a collection of largely critical studies at a time when the climate of opinion does not favour the critical, and when interest has swung from any living conception of medicine or physiology as branches of natural philosophy to a predominant preoccupation with new techniques and their rich harvest of new facts. That the harvest is rich it would not be candid to deny.

All the papers, except the address with which the series ends, are largely critical in character and content, dealing with certain limited and specific aspects of the anatomy and physiology of the nervous system as these are related to clinical neurology. Yet it may be submitted, not unfairly, that they are not merely critical, for they seek also to present certain fresh generalizations and to integrate the diverse material under consideration into new patterns that are not always in accord with those designed by the original authors whose work comes under review.

When we bear in mind, as we may so profitably do, the salutary and powerful influence which critical thought and writing have had upon the development of literature, and recall the stature of some of the figures who have been both outstanding critics and creative writers in literary history, it is with a strong sense of contrast that we recognize how rarely we meet the critical in the literature of science, and how minor a rôle it plays in our time. Even those suggestive and searching analyses of the nature of modern science that Whitehead has given us are not known to the generality of

scientists, though this may in part be due to the forbidding linguistic problems his writings present, and in part also to the lingering influence of that hostile attitude to philosophy that we see so dogmatically exemplified in Karl Pearson's "Grammar of Science." [1]

In any case, we may well ask ourselves whether, despite the many and obvious differences between literature and science, it can be altogether wholesome to find that the unresting collection of new facts in science is to so relatively slight a degree accompanied, or illumined, by the critical assessment and synthesis of all this new information, or at least by some deliberate search after synthesis. Here, surely, integration is not keeping pace with differentiation.

For new facts, or what claim to be such, the editor of the scientific journal has an insatiable appetite, but to anything in the nature of critical writing he is often found to be acutely allergic, and at the writer thereof he instinctively looks askance. In a forthright and penetrating lecture upon this subject, Dingle [2] expresses the view that "the extent to which recognition of an activity is tangibly manifested is a true index to the respect in which that activity is held, and a condition in which clear-sighted understanding is esteemed so lightly in comparison with blind achievement is not one which ought to be regarded without misgiving."

For too many amongst us, also, the inadequate conception that "science is measurement" and concerns itself with nothing but the metrical has become a thought-cramping obsession, and the more nearly a scientific paper approximates to a long and bloodless caravan of equations plodding across the desert pages of some journal between small and infrequent oases of words, the more quintessentially scientific it is supposed to be, though not seldom no

[1] In comment upon such an attitude Whitehead says: "All science suffers from the vice that it may be combining various propositions which tacitly presuppose inconsistent backgrounds. No science can be more secure than the unconscious metaphysics which tacitly it presupposes. . . . Thus the certainties of science are a delusion. They are hedged around with unexplored limitations." ("Adventures of Ideas," Cambridge University Press, 1933).

[2] "The Missing Factor in Science." Inaugural Lecture by H. Dingle, Professor of the History and Philosophy of Science in University College, London. H. K. Lewis, London, 1947.

one can tell—and few are interested to ask—whither in the kingdom of ordered knowledge the caravan is bound.

Whatever may be true of the physical sciences, the day is not arrived when all the truths of medicine and biology can be reduced to this bleak residue, or when living nature can be comprehensively expressed in what fashion decrees shall be called a protocol.

Darwin would have fared ill indeed under such a dispensation, for he offered neither equations nor formulæ to the science of the nineteenth century to adorn the fruits of his immense genius for natural philosophy.

Now even within the relatively small field of neurological study, using this term in its widest sense to include anatomy, physiology and neuropathology, knowledge has become so wide and so differentiated, and techniques of exploration so diverse, complex and exacting, that a synoptic and balanced appreciation has become as difficult as it is rare. None but the hardiest would now readily venture upon the labour of critical thinking or of writing outside the limits of his own special interest within it.

Yet surely it is vital that our understanding should be as comprehensive as possible, and essential that we should exercise an unremitting critical vigilance in assessing the published records of relevant thought and observation.

Now the training of the critical faculty upon which this must depend cannot begin too early in a scientific education, and in respect of medicine the case for it has been so cogently stated by Sir Thomas Lewis[1] that it may be useful to quote at length what he has to say: "Reform, to be useful, must render the student of medicine discriminating in a world where a disquieting proportion of what is offered him in conversation and in the generality of journals and of books is inaccurate, slovenly or redundant. . . . It is fundamental in medical, as in all other forms of education, that the student should acquire sound habits of learning. He should become acquainted with the history of discovery, coming to understand how knowledge has been and is being won; he should be taught to recognize sound sources of information, past and present; he should be taught to study steadily and intelli-

[1] "Reflections upon Reform in Medical Education." *Lancet*, 1944, 1.

gently; that he may come to possess that great acquisition of the student—namely, a fondness, or more exceptionally a passion, for understanding, and through this achieve conscious independence of thought and judgment. Understanding derives from an intelligent and discriminating study of past and present experiences; once attained it unbolts the doors to an understanding of further experiences. Discrimination of true from false relies upon a practised faculty of criticism, and upon a firm grasp of the rules of evidence. Understanding is the basis of progress and the vital flame in education; discrimination is the only sure defence against false doctrine and unsound practice." We may round off this long quotation by another and brief one from Dingle (*loc. cit.*), thus: "Criticism can no more prevent the emergence of the good than that of the bad, as the example of literature shows, but it can create an atmosphere in which the good flourishes and the bad withers."

But it is still not enough to have sound sources of information and to be able with confidence to distinguish the wheat from the tares. Facts, after all, are not science but only the raw material of that ordered knowledge which is science, and in the ordering of facts, in the capacity to choose the significant amongst them, to apply the inductive process to them and to make those syntheses which are the natural starting points for further planned experiment and observation, there also we find the highest rôle of the trained critical faculty. Observation is selection and thus implies the presence of directing ideas, of hypothesis. Long ago Hughlings Jackson, a true natural philosopher in medicine, observed that "we have multitudes of facts, but we require, as they accumulate, organizations of them into higher knowledge; we require generalizations and working hypotheses. . . . The man who puts two old facts into new and more realistic order deserves praise as certainly as does the man who discovers a new one. There is an originality of method."

What I have in mind as a natural extension of those qualities desired by Lewis in the student of medicine is more fully exposed in the last paper in this volume: an address

entitled "The Integration of Medicine," and need not be further elaborated here.

It would be impossible for the candid observer to deny that within the field with which the papers here collected seek to deal there is a large measure of truth in the indictment that Lewis has made in the passage quoted, for there is not a little in our literature that is inaccurate, slovenly and redundant, and, after all, our literature is but the expression of our thinking. To find examples is a task as easy as it is depressing. For instance, it would seem incredible, did we not know it to be true, that for approximately seventy years we have included within what purports to be a scientific nomenclature the term "giant cell of Betz." Yet at no time within that long period have we ever had a precise or commonly accepted definition of what the term referred to, nor any universal criterion by which the object so named could be certainly identified. Long assumed to be a specific morphological entity with specific functions, it is found to have as many metrical qualifications as there are writers who have written about it, and since there has been no agreement as to what constitutes a giant cell of Betz, there can be no agreement as to its distribution in the precentral cortex, or as to its rôle as the cell from which the pyramidal tract fibre has been said exclusively to arise.

On this unstable anatomical foundation, an hypothesis of the constitution and rôle of the motor cortex has been hopefully erected, with chaotic results that should not surprise us.

In the general field of cortical cytoarchitectonics a comparably vague state of affairs prevails, and the readers of a recent superb critical and constructive examination of the subject by Lashley and Clark[1] will find therein confirmation of the conclusion submitted in one of the following papers that this body of knowledge is to a grave degree illusory in its apparent precision, is based upon the study of an indequate number of samples by methods which lack any constant standards of observation and result in conflicts of statement that have gone far too long uncriticised,

[1] "The Cytoarchitecture of the Cerebral Cortex of Ateles: A Critical Examination of Architectonic Studies." *J. Comp. Neurol.*, 1946, 85, 223.

critic do not invalidate the principle that only the sharp and steady breeze of critical thought can keep the atmosphere of the laboratory, the clinic and the study fresh and wholesome and allow knowledge to grow undeformed therein to its full stature.

A prime purpose of this reprint, therefore, is to stimulate critical thinking amongst post-graduate students of neurology who may wish to penetrate more deeply into one or other aspect of this fascinating branch of medicine, and, when they sit down before the literature, to make of them gourmets rather than gourmands. I am persuaded that our work and our literature display too rarely the power of logical and sustained thought; the capacity to distinguish between thoughts, words and things in drawing conclusions and elaborating hypotheses; and, finally, the ability to make abstractions that are not vitiated by a neglect to consider relevant truths omitted in the process of abstraction. At times, indeed, it is no exaggeration to say our literature sinks to the level of the naïve, for sustained thought is an effort we engage in only under duress, as it were, and in a field of knowledge so vast and containing so much that is yet uncomprehended it is fatally easy to decline into facile allegory, and to be content with a medley of *ad hoc* hypotheses.

It is tempting, and a humbling exercise, sometimes to see the humorous side of our interests and activities, and in this mood it is not altogether inapt to say that there are chapters in neurological literature that might justly be styled "neuro-mythology." Examples of this have been mentioned and, I believe, it would not be difficult to add to them.

In conclusion, the reader of these papers could pay no greater compliment to their author than to read them, as they were composed, in a critical spirit. Six years have already passed since the first two of them were written, years in which, thanks largely to the work of Graham Weddell, our knowledge of the anatomy of cutaneous innervation has grown; in which Lashley and Clark's study of cortical cytoarchitectonics promises to open a fresh and more scientific chapter in that somewhat unsatis-

factory body of knowledge ; and in which the work of Gellhorn and his collaborators upon the motor cortex has shown with increasing clearness how unreal is the widely current conception of that cortex as being anatomically and physiologically a " mosaic."

It begins to appear possible that we shall understand the motor cortex better if we make some differentiation between it and the cells of origin of its main projection tract, the pyramidal system. A comparison between the second and the fifth paper of this series will indicate that the author has somewhat changed his view on this matter in the direction thus implied. There can be no finality in science, and the critical writer, if he does not learn as he goes, had better cease from his labours.

The Anatomy and Physiology of Cutaneous Sensibility

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Chapter I

The Anatomy and Physiology of Cutaneous Sensibility

Part I

CLINICAL-EXPERIMENTAL OBSERVATIONS

I.—Introduction

Nearly forty years have elapsed since the publication of Head and Rivers' paper, "The Afferent Nervous System from a New Aspect" (1905), opened a fresh chapter in the study of the sensory system, and gave a direction to subsequent studies and to our ideas on the subject that still remains dominant in neurological thought. Prior to Head's work there had been two main trends in the study of the sensory nervous system : purely physiological and morphological studies of the sensory end-organs in normal skin and of their functional qualities, and the predominantly anatomical studies of sensory nerve distribution in lesions produced by injury and disease. Head, feeling that the study of disordered sensory function had been subordinated to anatomical considerations and that it called for the same physiological methods that had been devoted to the study of normal cutaneous sensibility, turned to the investigation of the nature of sensory disorders and to their interpretation in terms of normal function ; at first as revealed in the clinical examination of the results of disease and injury of peripheral nerves, and later by the experimental method. As is well known, he caused a cutaneous nerve to be severed in his own forearm, and then with his collaborator Rivers proceeded to examine and analyse the disorders of sensory function immediately resulting, and to trace the restoration of sensory activity as the severed nerve regenerated. The method was essentially a physiological one, its prime object the determination of function. It was only secondarily concerned with structure.

In seeking to generalize from his observations, he came to postulate the existence of a double system of cutaneous sensory nerves and end-organs to which he gave the now familiar names of the protopathic and epicritic systems. His studies included no direct attempt to ascertain whether or not the skin actually contained these anatomical mechanisms, but it was concluded that they must exist to account for the physiological phenomena observed. The later and more exhaustive studies of Trotter and Davies (1909, 1913) on the sensory innervation of the skin were carried out by the same experimental method: namely, by cutaneous nerve sections on the observers themselves, but they did not find it necessary in the interpretation of their findings to postulate the existence of any anatomical structures not already known to exist. Still later, Boring (1916) again adopted this experimental method, and here, as in the two earlier series of observations the prime concern was to determine the nature of cutaneous sensory function rather than that of sensory structures.

More recently, Lewis (1936) has used the experimental method in the investigation of the sensory phenomenon of cutaneous hyperalgesia produced by local injury. Like Head, he has deduced the existence of a special system of nerves and end-organs in the skin to account for his findings, and these he has named "the nocifensor system of nerves." Although he specifically denies strictly sensory functions to these nerves, he associates them closely with the activity of sensory nerves, and therefore they may be considered here. Like Head, too, Lewis provided no direct evidence of the actual anatomical existence of the system of nerves in question. Therefore, both these observers may be said to subordinate the study of structure to that of function, and are ready to call into existence, as it were, anatomical structures to meet the apparent requirements of physiological observation. At a time when the state of knowledge of the sensory equipment of the skin was imperfect, this mode of deduction was perhaps justifiable and necessary, and it has certainly added valuable chapters to the body of neurophysiology. Yet there are manifest dangers in the method, or theories of function can never be regarded as soundly

based until they rest upon an assured foundation of ascertained structure.

It is important to note that the structures the existence of which has been postulated by Head and by Lewis are peripheral and not central. In the case of Head's theory of the constitution of the sensory system, the progressive elaboration of this system during phylogenetic evolution is believed to have been achieved by the multiplication of peripheral sensory end-organs and nerves ; thus, the epicritic system of nerves has been developed to amplify and control a more primitive protopathic system. Yet all that we have learned of the evolution of the nervous system encourages us to think that the elaboration and refinement of nervous function has been attained, not by any multiplication of peripheral organs, but by increasing differentiation and integration of function in the central nervous organ. Since its first appearance, the spinal cord has evolved but little, the peripheral nervous system probably even less.

It is therefore improbable that the development of sensory function can have been reached by anatomical additions to the peripheral sensory mechanisms. In his Gifford Lectures (" Man on his Nature," Cambridge University Press, 1940) Sherrington makes a reference germane to this point. " The naïve observer," he remarks, " would have expected evolution in its course to have supplied us with more various sense organs for ampler perception of the world. . . . The policy has rather been to bring by the nervous system the so-called " five " into closer touch with one another. A central clearing house for sense has grown up. . . . Not new senses, but better liaison between old senses is what the developing nervous system has in this respect stood for " (pp. 287-89).

Within the past few years our knowledge of the anatomical basis of cutaneous sensibility has advanced considerably, and Woollard (1940), by the use of a simple direct method of examination of sensory nerve fibres in the skin, has restored structure to its proper place in the study of the sensory nervous system. Electro-physiological methods in the hands of Adrian and others have also taught us much about the nature of the nerve impulse, and have forced us to

abandon the notion of sensory impulses of various specific qualities. The moment seems ripe, therefore, for a general review of our knowledge of the factors underlying cutaneous sensibility.

II.—Head and Rivers' Theory of the Afferent Nervous System and some of its Corollaries

In the classic series of studies on the sensory nervous system with which Head and his collaborators have enriched clinical neurology, three of the early papers were devoted to the peripheral nervous system. From their investigations of the sensory changes following upon injuries of various peripheral nerves, and more particularly from the minute study of an area of sensory loss experimentally produced on Head himself by the section of the radial nerve in his left forearm, Head and Rivers came to very striking and definite conclusions as to the constitution of the peripheral nervous system on the afferent side. Expressed at this stage as briefly as possible, their theory is that the cutaneous afferent nervous supply is dual and consists of two anatomically and physiologically distinct systems of receptive end-organs and conducting neurones. One of these, which they call the *protopathic system*, is more primitive both in its origin and in the nature of its activity than the other, or *epicritic system*, which becomes the dominant partner with reactions of considerable refinement. In addition to these two purely cutaneous systems the structures deep to the skin have their own sensory nerve supply. The peripheral afferent nervous system consists, therefore, of three fibre systems. The division of function between them and the relations in which they stand to one another, as described by Head and Rivers, form one of the most complex chapters in the physiology of the nervous system, and one which, if we accept their theory, is of fundamental importance.

In later studies, Head and his co-workers traced the passage of afferent impulses through the spinal cord until they finally reach the highest centres and enter into consciousness to form the basis of sensation. Into each of these studies the theory of the constitution of the peripheral

nervous system to which brief reference has been made was woven, and with the publication of the last of these, that on "Sensation and the Cerebral Cortex," took a permanent place in Head's conception of the whole afferent nervous system.

Yet the implications of this initial conception of the peripheral sensory endowment were to be extended still further, for in the course of his investigation with Riddoch of the reflex phenomena of the divided human spinal cord, Head (H., p. 467) came to the conclusion that the reflex activity of the isolated portion of the cord shows the general features characteristic of the reactions of the protopathic system. The "mass reflex" which they described in spinal man seemed to them to present the counterpart on the motor side of protopathic sensibility. Thus arose the conception of a primitive animal form endowed with an entire nervous system of protopathic quality. Lastly, in his book, "Instinct and the Unconscious," Rivers (1920) boldly attempted to construct a biological theory explaining the primitive instincts and the genesis of the psychoneuroses on the analogy of a protopathic nervous system.

Clearly, therefore, the importance of Head's original theory of the sensory nervous system is far-reaching, for it must influence our entire conception of the development, structure and functions of the nervous system. Its foundations must therefore be closely scrutinized. There are several ways in which this task may be approached, but they are not all equally open to us. Thus, the value of the facts of observation recorded by Head and Rivers can be assessed fully only by those who repeat them. This was done by Trotter and Davies (1909, 1913), whose findings and conclusions differed in essential respects from, and are on record for us to compare with, those of Head. However, there are other avenues of approach to this complex problem that do not appear to have been fully explored as yet. Firstly, we may study the theory as formulated by Head and try to determine whether it is the simplest and least speculative generalization of the recorded facts. Secondly, we may examine the final conception of the development and activity of the afferent nervous system proposed, in the

light of the general body of physiology and biology. Thirdly, we may take the "protopathic animal" and attempt to determine its possible place, if any, in the evolutionary series.

(i) *The Peripheral Sensory Mechanism*

According to Head and Rivers, section of a cutaneous nerve results in the production of an area of altered sensibility with a sharply defined border within which the skin is wholly insensitive to cotton-wool touch (*cf.* diagram, p. 31). Situated more or less centrally within this area is a region which is, in addition, totally insensitive to painful and thermal stimuli and is surrounded by an intermediate zone of skin (between it and the margins of the area of tactile anæsthesia) sensitive to painful stimuli (pin-prick) and to extremes of temperature (above 37° C. and below 26° C.) but anæsthetic to cotton-wool touch. Sensibility to painless and painful deep pressure remains intact throughout the entire area of cutaneous change, and the capacity of localizing the spot pressed remains unimpaired. However, the two points of the compass simultaneously applied to the skin (Weber's test) cannot be discriminated at all within the area of tactile anæsthesia. Further, the sensibility of the intermediate zone is not only diminished in range as compared with normal sensibility, but it is also qualitatively different from that possessed by normal skin. Thus, the prick of a pin is abnormally painful and arouses an almost irresistible desire to withdraw the part pricked. Also, the pain is diffuse, radiates and cannot be accurately localized.

When it begins, regeneration was thought to occur in two stages, widely separated in point of time. The first stage consisted in the gradual development within the central area of the mode of sensibility possessed from the outset by the intermediate zone. Thus, painful stimuli and extremes of temperature were perceived through the entire area by the end of seven months from the date of section of the nerve. The qualitative sensory alterations previously noted in the intermediate zone were also present throughout the area ; the pain of a prick was intolerable, cold was unduly cold and warmth unusually pleasant. Further, a

form of tactile sensibility began to appear. When hair-clad skin within the affected area was stimulated by cotton-wool a diffuse, tingling and referred sensation was perceived. When the skin was shaved this sensory quality disappeared. Head speaks of this as a peculiar form of "hair sensibility" belonging to the protopathic system. A threshold above the normal was observed for all these sensory qualities, and there was radiation and inability to localize stimuli.

According to Head, this range of sensory functions is subserved by a system of punctate end-organs in the skin: pain, heat and cold spots and hairs. Many months after the full establishment of this state of affairs, the second stage of restoration of function begins. The diffuse, radiating and non-localizable quality of sensations disappears, the threshold lowers to normal, the over-response abates and sensibility to cotton-wool touch begins to reappear, and with it the capacity to discriminate two simultaneous contacts. It becomes possible to discriminate thermal stimuli of temperatures less removed from that of the skin than formerly. Finally, all sensations aroused come to bear a close relation to strength of stimulus. To generalize all these phenomena of sensory loss and recovery, Head and Rivers evolved the hypothesis that the sensory mechanism of the peripheral nerves consists of three anatomically distinct systems of nerve fibres and end-organs.

(*a*) *Deep Sensibility.*—This responds to moving stimuli and to painful or painless degrees of pressure. The fibres of this system are distributed with the motor nerves, and are therefore not interfered with by section of a cutaneous nerve. This form of sensibility remains intact when a purely cutaneous nerve is divided.

(*b*) *Protopathic Sensibility.*—This is the sensibility of the intermediate zone and of the whole area at the end of the first stage of regeneration. It is also the sensory state of the normal skin covering the glans penis. It responds only *to painful cutaneous stimuli and to extremes of heat and* cold. It includes also a form of hair sensibility distinct from light touch. It has a high threshold and the sensory response is maximal, ungraded, diffuse and erroneously referred.

(*c*) *Epicritic Sensibility.*—This is a sensibility to light touch, to intermediate grades of temperature (between 22° and 40° C.).[1] It includes the capacity to localize single and simultaneous two-point tactile stimuli. It is a low threshold mode of sensibility.

Therefore purely cutaneous sensibility is subserved by two mechanisms, and since in a given nerve the area of epicritic supply is apt to be greater than that of protopathic sensibility, the division of the nerve provides a spatial dissociation of the two modes of sensibility, a narrow zone of pure protopathic sensibility (the "intermediate zone") surrounding the central area of cutaneous anæsthesia. There is also a temporal dissociation, since the protopathic mode is restored earlier than the epicritic (in terms of anatomy, the protopathic fibres regenerate more rapidly than the epicritic), and a stage is reached when the entire area of sensory change is innervated solely by protopathic sensibility. That is to say, the sensory qualities exhibited by *the intermediate zone immediately after nerve section* are identical with those shown by the entire area at the end of the first (protopathic) stage of regeneration. The later regeneration of epicritic fibres provides a second stage in the restoration of function. Further, the disappearance of the peculiar qualities of protopathic sensibility, namely, maximal ungraded response, diffuseness and absence of localization, when epicritic regeneration is complete, is said to prove that the epicritic system inhibits or dominates the protopathic; a conclusion that allows us further to suppose that the protopathic is a primitive mechanism of earlier phylogenetic development than the epicritic system.

It has been mentioned that nothing is directly known of the structures postulated by Head in his hypothesis of a dual sensory mechanism in the skin, and the form assumed by these in his exposition seems to be determined by what Head conceived to be structural necessities of the functions he was investigating. Pain, a purely protopathic mode of sensibility, is subserved by punctate end-organs, the pain spots. Protopathic thermal sensibility is said to be subserved by the "heat" and "cold" spots that earlier investigators

[1] Head gives varying figures on this point in his different expositions.

had noted, but epicritic heat and cold are believed by Head to be subserved by some non-punctate system of end-organs, the morphological characters of which he nowhere discusses. Tactile sensibility (light touch) is subserved by the punctate touch spots belonging entirely to the epicritic system. In hair-clad skin these are grouped round hair bulbs, but in hairless skin—such as the finger tips—they are so closely grouped in the skin that it is difficult to demonstrate their punctate character. In addition to these epicritic touch spots, which Head says are not analogous with pain, heat and cold spots (though how they differ is not stated), there is a peculiar form of protopathic tactile sensibility, called "hair sensibility," which appears to employ the same end-organs as epicritic touch. The qualities of protopathic hair sensibility are its lack of accurate localization and a peculiar tingling quality. How a single type of end-organ can subserve these separate and differing modes of sensibility is not explained. This arrangement is most easily seen in tabular form :

Pain :	Punctate end-organs (pain spots) . .	Protopathic.
Thermal sensibility :	Punctate end-organs {heat spots, cold spots} . .	Protopathic.
	Non-punctate end-apparatus of unspecified nature	Epicritic.
Touch :	Punctate end-organs (touch spots) . .	Both epicritic and protopathic.

That the primary modes of cutaneous sensibility should be regarded as being dealt with by the nervous system in this discrepant manner suggests that the exigencies of hypothesis have borne too hardly upon the facts : an impression that is not lessened when we learn, as will be seen, that when they reach their first synaptic junction in the spinal cord, the qualitatively distinct nerve impulses assumed to be generated in this odd assembly of end-organs lose the specific qualities that it is the latter's prime function to confer upon them. This, summarized, is the theory of the constitution of the peripheral sensory system formulated by Head and Rivers.

It is now necessary to examine how this anatomical background must influence the manner in which impulses arising in these cutaneous systems are integrated within the

organs of the protopathic, epicritic and deep systems, "each impulse," according to Head, "being stamped with the characteristics peculiar to the end-organ in which it has arisen" (H., p. 644). In particular, the protopathic impulse is said to be "heavily charged with feeling tone." Yet we now know that the individual sensory nerve impulse shows no evidence of any specific qualities, and could not in any case possess the psychological quality of "feeling tone."

Nevertheless, let us examine what is actually postulated of specific combination. By it all sensory impulses reaching the spinal cord are sorted into new pathways, each of which subserves a special mode of sensibility: tactile, thermal, painful or postural. Thus, "the afferent consequences of all stimuli capable of evoking a sensation of heat, whether of epicritic or of protopathic origin, are gathered together into special secondary tracts. The entrance to these is guarded by specific 'intramedullary receptors' which, like resonators, are attuned to pick up one particular quality of impulse" (H., p. 651). Further, "when an impulse which has originated in the effective stimulation of a heat spot belonging to the protopathic system reaches an intramedullary receptor of the secondary system set aside for impulses of heat, it starts a specific impulse. But the same receptor reacts to the epicritic impulses which are started by stimulation of the skin with temperatures between 32° and 40° C." (H., p. 404). Thus, it is inevitable that the specific qualities attributed to protopathic and epicritic impulses should disappear when a common secondary pathway is entered. It is not easy to see what rôle is now left for selective inhibition, or what can be the nature, or what the necessity, of a process by which epicritic sensibility achieves its dominance over a special variety of protopathic impulse that, we are told, loses its characteristics spontaneously when it enters the secondary pathway. Despite this, it is clear from other expositions of the theory that the special qualities of the protopathic impulse are required to survive until the end station in the thalamus has been passed by the ascending impulses.

Anatomically, the rearrangement is said to be as follows: Impulses subserving thermal and painful modes of sensi-

bility enter the secondary path upon their entry into the cord ; this path decussates and turns upwards in the crossed lateral column (lateral spino-thalamic tract). Impulses subserving postural sensibility and tactile sensibility (including two-point discrimination) do not enter the secondary path at once, but turn upwards, still in the primary neurone, in the posterior column of the side of entry. They meet their synaptic junction at the posterior column nuclei of the medulla and, entering the secondary path which decussates at once, undergo a regrouping in which postural impulses, tactile impulses and separate impulses subserving two-point discrimination all travel in distinct secondary paths. But tactile impulses exist of another order. These, subserving the sense of touch and localization, are rapidly filtered off into a secondary path which decussates and turns upwards in the crossed half of the cord in the ventral spino-thalamic tract.

Specific combination is thus completed, and all modes of sensibility are now travelling in secondary pathways grouped as follows : (i) postural ; (ii) thermal ; (iii) painful ; (iv) impulses subserving the sense of touch ; (v) impulses subserving single spot localization ; (vi) impulses subserving two-point discrimination. It should be noted that the two last categories do not subserve the appreciation of touch, but only the qualities named.

Consideration reveals that this remarkable process, though avowedly only an anatomical rearrangement, has effected (or is presumed to have effected) qualitative changes in sensory impulses, and has abstracted from tactile impulses two of the qualities of normal tactile sensibility. Thus, the deep afferent end-organs normally respond to deep pressure and possess the capacity of localizing a single pressure stimulus, but they lack the capacity, according to Head, of two-point discrimination (Weber's compass test). Tactile end-organs subserve light touch, localization and two-point discrimination. Yet once the impulses arising in the two sets of end-organs concerned enter the secondary pathway "all distinction is lost between those arising in different peripheral systems. The lightest touch and the heaviest pressure, short of discomfort, form the two ends of a

graduated tactile scale" (H., p. 655). That is to say, a qualitative identity has been conferred upon sensory impulses that prior to spatial regrouping were not identical in character. Even more profound is the effect of specific *combination upon tactile impulses, for once the secondary* path is entered, localization and two-point discrimination each has its own anatomical pathway distinct from that subserving the appreciation of touch.

Now, as a mental act on the observer's part it is possible to abstract separate qualities from a single natural function. Thus, we can *think* of tactile sensibility, localization and two-point discrimination as abstractions and separately, but they cannot exist apart in nature. There is no such *thing* as localization or discrimination, there are only things localized or discriminated, and we cannot conceive of an impulse that allows us to localize or to separate without making us aware of the things localized or separated. This conception of sensory functions clearly embodies a confusion of thoughts with things, and even though clinical examination should in a given case of sensory alteration reveal apparent dissociations of these three aspects of tactile sensibility, we cannot account for such dissociations in this way. In short, the notion of pathways for localization or for discrimination are in the same category as that of pathways for truth or beauty, and are but figments of the observer's mind. Two-point discrimination presupposes the simultaneous stimulation of spatially separated end-organs in the skin and subcutaneous tissues. From each end-organ thus excited, volleys of separate impulses must travel by different nerve fibres to the highest cortical centres, there to form the basis of a discriminating judgment. That a multiplicity of end-organs probably underlie two-point discrimination is to be inferred from Trotter's observation that excitation of cutaneous tactile end-organs alone is inadequate to secure accurate two-point discrimination: deep end-organs must also be stimulated. While, as quoted by Trotter, Spearman found that this discrimination waned in acuity in the presence of muscular fatigue. Therefore, cutaneous, subcutaneous and muscular afferents probably all combine to provide the sensory material out of which discrimination is achieved.

In other words, it is a judgment and not a mode of sensibility: a judgment made as a result of integration in the only place where such integration can occur, namely, in the cerebral cortex. Head (H., pp. 392-95) provides evidence of this order, when he finds that posterior column lesions impair two-point discrimination and postural sensibility together, while Holmes (1927) has pointed out that disturbance of discrimination of one from two-point stimuli is frequently the most striking effect of a lesion involving the sensory cerebral cortex: another indication of the cortical seat of the physiological processes involved.

As for localization, it does not appear from Head's clinical records that there is any necessity or justification for postulating a divorce of contact sensibility from localization. The cases he believes to reveal this separation do not unequivocally do so. These cases consist of (i) one of glioma involving the mid-brain where the most that could be stated was that the disturbance of localization was "out of proportion to the disturbance of tactile sensibility," and (ii) of 24 cases of the thalamic syndrome in which the majority showed defects in tactile sensibility, but only 12 cases showed comparable defects in localization. In other words, tactile sensibility was found disturbed more frequently than localization, but it is not recorded that the latter was defective when the former was normal. In short, a significant dissociation of localization from tactile sensibility appears not to have been noted.

In conclusion, then, as elaborated by Head, specific combination is an incredible function. The rôle and nature of selective inhibition are equally difficult to understand. The protopathic thermal impulse with its heavy charge of "feeling tone," its radiation and erroneous localization, having reached the thalamus has to be appropriately modified by the coincident epicritic thermal impulse. The aspect of thermal sensibility subserved by the former is believed to reach consciousness in the thalamus, while epicritic thermal sensibility is a function of the sensory cerebral cortex. How does the latter prevent the undesirable qualities of the former reaching consciousness? There seems no alternative but to suppose that the cortical control

of thalamic sensibility *is* the epicritic control of protopathic sensibility. Yet, clearly, this is not Head's view, and if it were so the sensory features of the thalamic syndrome should be those of protopathic sensibility as revealed in the intermediate zone after peripheral nerve section. Yet, again, thalamic sensibility is not identical with protopathic sensibility, and it is not possible to discover in what selective inhibition really consists and how it is achieved. Rivers, conscious of the difficulty, supposes that thalamic sensibility differs from protopathic, because the characteristic features of the latter are inhibited at the periphery. Yet this notion runs counter to our knowledge that in the cerebrospinal nervous system, inhibition is a central and not a peripheral function. In short, no provision is made in Head's hypothesis for the attainment of epicritic dominance, and the reader arrives at the final stage of this hypothesis with a profound sense of confusion.

In short, as we trace this hypothesis from its beginnings to its ending, we find it increasingly and, at last, fatally embarrassed by the necessity of weaving into its fabric the dual peripheral sensory mechanism with the hypothecation of which it began. Speculative anatomical structures different for each mode of sensibility, and physiological processes inconceivable in nature and often mutually exclusive, have to be assumed from stage to stage in the endeavour to harmonize the initial with the final stages of the hypothesis, so that the complete form taken by this wholly lacks coherent meaning. This is not to say that the impressive body of observations upon the sensory changes that ensue upon lesions of the spinal cord, brain-stem and cerebral hemispheres that we owe to Head is not a great achievement and a notable contribution to neurology; it is simply to submit that Head's generalizations from these observations are unsatisfactory and do not provide a theory of the afferent nervous system that we can accept. Yet despite the fallacies that we may think we detect in the interpretations advanced by Head, the crux of any criticism of his work must lie in the detection of errors of observation. In respect of the sensory changes ensuing upon lesions of peripheral sensory nerves, it has to be admitted that no

subsequent observer has confirmed Head's findings in certain essential details and that no convincing evidence of a dual peripheral sensory mechanism can be found. His theory of the afferent nervous system must, therefore, be rejected on factual as well as on theoretical grounds.

(iii) *Dissolution of Function in Disease and Injury of the Nervous System: Jackson's Hypothesis and Head's Interpretation of it.*

It is the fascination of Head's theory that it constantly brings the student up against fundamental general principles in biology and neurophysiology. In this attempt to generalize from his observations of sensory and motor disorders, we meet an important general principle.

To understand how Head and his collaborators have reached their significant conclusions, it is necessary to consider the method they adopted in their approach to the problems of cutaneous sensation. Briefly, all the work on the afferent nervous system we have reviewed is based upon the study of residual sensibility. In the case of a nervous lesion affecting sensation we have to study not only the degree and nature of sensory loss ensuing, but also the nature of such sensation as remains. Now, Head and Rivers, in investigating the area of altered sensibility resulting from the nerve section on Head's forearm, believed that they were able to distinguish by the method of residual sensibility a dissociation of normal sensibility into deep and cutaneous systems. Further, the study of the intermediate zone of the area of altered cutaneous sensibility, and of the alleged two-stage regeneration, led them to conclude that there were two systems of cutaneous innervation, protopathic and epicritic. Similarly, in tracing the path of sensory impulses from their point of entry into the central nervous system to the highest centres, the same method of residual sensibility was employed to discover the specific combination and the selective inhibition of sensory impulses—in short, their integration before they come to appear in consciousness as sensations.

The entire nervous system reacts to injury of one of its component parts, and the mutilated residual innervation

remaining is itself probably composed of several factors and is capable of resolution into elementary components. What is the significance of this residual innervation? In considering this question we are at once reminded of Hughlings Jackson's teaching upon the dual nature of nervous symptomatology and upon the mode of dissolution of function in the nervous system. Upon the former point the principle he enunciated was admirably summarized by Broadbent as follows: The functions of a centre in which a lesion has occurred are suspended, and corresponding symptoms may be called negative. These are, however, not the only symptoms; others, usually more obtrusive, and often infinitely more important, are produced by the activities of other centres, either (i) unbalanced in consequence of the absence of normally opposing activities, or (ii) liberated from the control of higher level centres, or (iii) intensified by attempts to compensate for the missing function. Nervous disease therefore effects a reversal of evolution. "Dissolution is a process of taking to pieces in the order from the least organized, the most complex and the most voluntary towards the most organized, the most simple and the most automatic," and again, "dissolution being partial, the condition in every case of it is duplex. The symptomatology of nervous diseases is a double condition; there is a negative and there is a positive element in every case. Evolution not being entirely reversed, some level of evolution is left." Hence the statement "to undergo dissolution" is rigidly the equivalent of the statement "to be reduced to a lower level of evolution" ("Selected Writings of John Hughlings Jackson," 1932, vol. 2, p. 46). It is to be noted, however, that Jackson nowhere suggests that the lower planes of evolution exposed by disease or injury necessarily represent physiological states that in earlier stages of phylogenetic evolution were the normal endowments of primitive nervous systems, nor did he suggest that dissolution of function was associated with the release of primitive anatomical systems to resume their original activities in their pristine form.

That Jackson's generalizations have been, and will continue to be, of the greatest importance to neurological thought will not be disputed, and his conception of the

release mechanism is perhaps one of his most valuable contributions. Yet it may be questioned whether sometimes too much has not been demanded of it. As commonly applied, there is no place for qualitative changes in function apart from simple increase or defect. There may well be perversions of function not thus easily to be generalized. In short, generalizations are dangerous in proportion to their value unless they are constantly correlated with the facts of observation. As Trotter (1913) has observed: " In dealing with theoretical considerations concerned with the physiology of the nervous system, one is exceptionally liable to be misled by preconceived or introspectively evolved notions as to how sensory and perceptive processes may be supposed to act. Symmetry and the desire for classification are apt to be mistaken for physiological principles, and we tend to drift into the error of supposing that conceptions which are clear cut, easily comprehensible and 'reasonable' acquire by that very fact an increased probability of being accurate expositions of the physiological processes they profess to explain. This has been repeatedly demonstrated in the history of neurology."

With these considerations in mind we return to Head's view that protopathic sensibility is " the level of evolution left" when a higher level epicritic system is out of action. It thus represents a primitive form of sensibility unmasked after its continuous suppression for countless ages in phylogenetic history. This being so, are we to assume that it is now revealed precisely as it originally was, or has its long suppression so modified it that what now appears resembles nothing that previously existed? If such a modification has taken place, how shall we determine its degree and kind? How can we even know that it has taken place? In truth we cannot know any of these things. On the other hand, if we are to assume that it now approximates in characters to a normal primitive sensory function, it should provide valuable information as to the mode of evolution of function in the nervous system.

Rivers (R., pp. 22-33) states that protopathic sensibility —and the mass reflex—do represent the reappearance of once normal forms of primitive nervous activity. Head's

views are exemplified by the following quotations: "The final act of sensation can be decomposed by changing its physiological components. The form assumed by such dissociation may resemble nothing that has previously existed in the phylogenetic history of man; or the change may approximate to the character of some more primitive activity. This is the case with high-grade protopathic sensibility and with sensations from the glans penis" (H., p. 8). Against this, we read (H., p. 743): "Removal of epicritic sensibility exposes the activity of the protopathic system in its full nakedness. In the same way, when removal of the influence of the cortex cerebri sets free the optic thalamus from control, sensation assumes an overwhelmingly 'thalamic' character. In each case a more primitive organization is kept under control by the activity of a higher afferent system. But removal of the dominant mechanism does not reveal the functions of the phylogenetically older organs in all their primitive simplicity. A lesion which sets free the human thalamus produces a highly specialized series of phenomena, which have never existed in this form in phylogenetic history." Again (H., p. 745): "many lower activities are retained in a controlled form and are not abolished in the course of evolution because they may be required at some time or another for their primitive purpose." But although thus controlled the primitive mechanism "must remain in full activity, ready to play its part, should occasion arise, in the defence of the body against noxious influences."

Surely, if these primitive functions may have to resume their original activity fully, as Head supposes, they must retain their original characters and not reappear in a form "which has never existed in phylogenetic history." A comparable conflict of statement informs Head's elucidations of the "mass reflex," for while this is not to be regarded as "reproducing an ancient mechanism in its primitive form," it is said to "reappear in its primitive form" immediately the spinal cord is transected.

Apart altogether from these inconsistencies, we may well ask whether we can accept the notion of an inhibition that has persisted uninterrupted throughout the countless ages

of phylogenetic history, and yet remains an immediately reversible phenomenon.

Nevertheless, it is clear that Head's theory of the afferent nervous system does in effect require that both protopathic and thalamic sensibility, as well as the mass reflex, should all be regarded as unmasked forms of primitive nervous activity, not essentially changed by their age-old suppression.

No hypothesis largely dependent upon phylogenetic considerations can ever be capable of scientific proof, yet it may well have the compensating attraction of being equally incapable of disproof, and there are always some who are ready to accept an hypothesis upon these equivocal terms. This readiness has been indicted by Karl Pearson in his "Grammar of Science" thus: "It is easy to replace ignorance by hypothesis, and because only the attainment of real knowledge can in many cases demonstrate the falseness of hypothesis, it has come about that many worthy and otherwise excellent persons assert an hypothesis to be true because science has not yet by positive knowledge demonstrated its falsehood."

(iv) *The Phylogenetic Significance of a Protopathic Nervous System*

Having seen the necessarily speculative nature of hypotheses that invoke phylogenetic factors, we may consider briefly the hypothetical protopathic animal. On the sensory side it possesses a sensibility that presents "none of those characters of sensation by which we recognize the nature of the (stimulating) object, no power of distinguishing difference in intensity, nor of telling with exactness the spot stimulated" (R., p. 23). "It would have no necessity for the discrimination which would enable the exact perception of the nature of the object" (R., p. 30). In fact, its sensibility possesses "elements of vagueness and confusion wholly incompatible with the exact power of localization." On the motor side the animal is not less handicapped, for in the mass reflex, which exemplifies its characteristic mode of movement, "the situation of the stimulus does not determine the distribution of the response." The mass reflex consists of powerful

bilateral flexion of the limbs, contraction of the abdominal muscles, evacuation of the bladder and an outburst of sweating. This response is not adapted to the strength or site of stimulation, but is maximal and unvarying, yet Head speaks of it as "an excellent answer to noxious stimuli in the lower animal"; able to respond only by a mass movement, the animal is "fixed in a position unfavourable to flight and crawls into a hole to die or recover" (H., p. 753).

Such a creature, even if it could take the steps necessary to propagate its bewildered kind, which appears doubtful, could have no survival value, for on receipt of a stimulus which it could not localize, from a stimulating agent whose nature it had no means of discovering, it could respond only by curling up and micturating. Yet this is the animal that Head and Rivers present to us as our common ancestor.

It is not necessary to pursue this line of thought further, or to consider the theory of instincts and of the genesis of the psychoneuroses elaborated by Rivers upon a foundation so unrelated to nature.[1]

Perhaps a more conclusive and less dialectical criticism of the protopathic nervous system may be found when we come to consider the reactions of the simplest forms of nervous system known to biologists. Parker has described such a one in the polyp, Corymorpha. Describing this creature, Parker (1919) says: "If a faradic stimulus is applied to one side of the stalk next the hydranth or the base, the stalk simply shortens as a whole. If, however, the stimulus is applied to one side of the stalk nearer the middle of its length, the stalk bends to that side and usually presses the hydranth with great accuracy against the spot. This response is not only appropriate for the particular side stimulated, but also in most cases for the given level of the stimulated spot on that side. . . . The success of this form of protective response naturally depended upon the accuracy of the localization." Here, therefore, the most primitive of animals appears already to have sensation of "epicritic" quality. Nowhere in nature, in fact, do we find a nervous system in any way comparable with the "protopathic"

[1] This theory has been discussed elsewhere by the present writer, *cf. Med. Sc.*, 1922, 6, 216.

system of Head and Rivers. As Sherrington has pointed out, a simple act of co-ordination may be as perfect as a highly complex one. The prime function of the nervous system is integration, as we have learned from Sherrington, and the terms "primitive" and "crude" so repeatedly employed by Head and by Rivers cannot properly be applied to even its simplest activities; they are, in fact, terms that create an impression in the reader's mind, but convey no information. At every stage of its evolution, as exemplified in the extant animal kingdom, the nervous system is seen to be an instrument of precision. It is its very nature and purpose to be such, and the conception of a protopathic nervous system as outlined by Head and Rivers runs directly counter to all we know of biological processes as these are to be seen in the evolution and activity of the nervous system.

III.—The Observations of Trotter and Davies on Cutaneous Sensibility

These were more exhaustive than those of Head and Rivers in that no less than seven cutaneous nerves were divided at intervals of time in two subjects. It was thus possible to make adequate immediate comparisons of the consequences of nerve section at all periods after the division. There was no necessity to rely, as in Head's case, upon the sensations of a single observer, or upon his memory in comparing the immediate sensory results of nerve section with those of the stages of regeneration. The importance of this enhanced opportunity for the control of what are peculiarly difficult observations and unfamiliar subjective judgments is manifest. These observations were published in two papers: "Experimental Studies on the Innervation of the Skin" (*J. Physiol.*, 1909, 38, 134) and "The Peculiarities of Sensibility found in Cutaneous Areas supplied by Regenerating Nerves" (*J. für Psychol. u. Neurol*, 1913, 20, 102). It is unfortunate that the latter paper has remained so unfamiliar to English-speaking neurologists, for it is an essential complement to the former.

In so far as Trotter employed the technique of investigation used by Head, his observations seem at first not to

present any essential difference from the latter's, but differences there clearly are and they prove to be of fundamental importance when conclusions come to be drawn from them. With the employment of additional methods, it appeared that changes in cutaneous sensibility not discoverable by Head's methods were present, and thus a still wider departure from his generalizations became necessary. In brief, Trotter was unable to confirm Head's description of the sensory qualities of the intermediate zone; nor the qualitative identity of this with the state of the affected area at the end of Head's first stage of regeneration; nor, in conclusion, did Trotter find that regeneration takes place in two stages.

A preliminary idea of the discrepancies between the observations of the two may be gained from the facts concerning thermal sensibility in the intermediate zone of Head. Head does not state whether the thermal stimuli in the intermediate zone give rise to thermal sensations of normal intensity: as they should do were these sensations a function of an intact protopathic thermal system—as by definition they are. Trotter finds that this so-called thermal sensibility to extremes of temperature is in fact a hypoæsthesia: stimuli which on normally innervated skin give a sensation of "hot" or "cold," giving sensations of "warm" and "cool" only. This finding is incompatible with Head's hypothesis. Further discrepancies will be referred to in due course (*cf.* diagram on p. 31).

In a preliminary discussion, Trotter points out that although graduated punctate stimuli may be necessary in the investigation of sensory function, yet such stimuli are not physiological in the sense that the surface of the normal organism under normal conditions does not receive single stimuli of this nature, but more widely distributed and qualitatively multiple stimulations, often affecting simultaneously end-organs of diverse kinds. In accordance with this principle it is found that the most accurate way of delimiting the external margins of an area of altered skin sensibility after cutaneous nerve section is to let the subject *stroke the skin with his own finger. In this way a larger* area of change is found than the most carefully graded

punctate stimuli (tactile stimuli) suffice to determine. Stroking is at once a more physiological and a more delicate mode of stimulus than a von Frey hair.

(i) *The Immediate Consequences of Nerve Section*

Briefly stated, the following are, according to Trotter, the immediate consequences to cutaneous sensibility of the section of a cutaneous nerve. The area of altered sensation consists of an outer zone of partial, and a central area of total, cutaneous sensory loss. The outer zone is delimited most accurately by the stroking method already described. No other method gives so precise a record, or one more constant on repeated examination. Within the margin thus detected, and as stimulation approaches the central area there is found a progressively deepening hypoæsthesia to *all* modes of cutaneous sensibility. The findings may be further particularized : *The hypoæsthetic zone :* Externally this is an area of qualitative change only. Von Frey hairs may give no clear indication of the peripheral limits of the area, but to stroking the skin feels smoother, and tickle, when it is elicited, less intense. Within this region, as the observer passes from periphery to central anæsthetic area, a margin is reached within which the skin feels subjectively numb and cotton-wool touch or light strokes with a camel-hair brush elicit no tactile sensation whatever. In this zone, the threshold of tactile sensibility to von Frey's graduated hairs rises, but a threshold can be obtained and there is hypoæsthetic tactile sensibility. Finally, as the central area is approached this threshold rises rapidly until the characteristic sense of a touch is lost as this area is reached.

Also within the surrounding hypoæsthetic zone, the threshold of two-point discrimination rises rapidly, but a threshold is always obtainable even in the central anæsthetic area as long as deep pressure sense remains. Trotter finds, also, that contact with a light hair, insufficient to stimulate deep pressure end-organs, does not give precise two-point discriminatory capacity. This is yielded only by combined stimulation of tactile and of deep pressure end-organs.

Another point of importance arises here. Head, in testing tactile cutaneous sensibility, used a fixed-stimulus

method: namely, a wisp of cotton-wool, believing that stronger stimuli excited the end-organs of the deep afferent system and not the cutaneous tactile end-organs (touch spots). As a result of this, all grades of tactile sensibility of higher threshold than that of cotton-wool passed undetected by Head. Trotter maintains that cutaneous "touch" is introspectively a distinct mode of sensation, easily differentiated by the subject from the sensations aroused by "pressure" acting on subcutaneous end-organs, and thus he felt himself free to use graduated punctate stimuli (von Frey's hairs) believing that sensations of pressure could be readily differentiated from those of true touch. Acting on this basis, Trotter finds that the hypoæsthetic zone possesses true tactile sensibility.

In respect of thermal sensibility in the hypoæsthetic zone, Trotter draws attention to a point of fundamental importance nowhere recognized by Head. He finds that normally innervated skin yields no response to temperatures within 5° C. of the skin temperature. There is thus an indifferent range of 5° C. on each side of this temperature: that is, a total indifferent range amounting to some 10° C. Thermal hypoæsthesia is expressed in two ways: (i) by a widening of the indifferent range to about 10° C. on each side of the skin temperature: that is, an indifferent range extending over from 15° to 20° C. of the thermometric scale, and by (ii) the diminished intensity of the thermal sensations appreciated outside this indifferent range. What is hot on normal skin is only warm in the hypoæsthetic zone, and what is cold on normally innervated skin is, in the hypoæsthetic zone, only cool. This significant finding may be expressed in diagrammatic form (Fig. 1). The cross-hatched area is the indifferent zone.

Trotter believes that the sensations hot and cold are a combination of warm plus pain and cool plus pain, and points out that at both ends of the thermal scale when supramaximal stimuli are used the sensation felt is pure pain.

In respect of painful sensibility in the hypoæsthetic zone, Trotter finds a comparable state of affairs, that is, a deepening hypoæsthesia as the central area is approached. The defect in sensibility is precisely similar to that for touch, heat and cold.

The hyperalgesia so stressed by Head in his intermediate zone is not constantly present. Immediately following nerve section there is a transitory hyperalgesia for some hours, then a period of about ten days in which no hyperalgesia whatever is present, and then a period of secondary hyperalgesia persisting for some six weeks. This then ceases entirely and for the two or three weeks that yet remain before the first indications of regeneration appear there is no trace of hyperalgesia. When present, this secondary hyperalgesia differs from that described by Head, in that it is very patchy

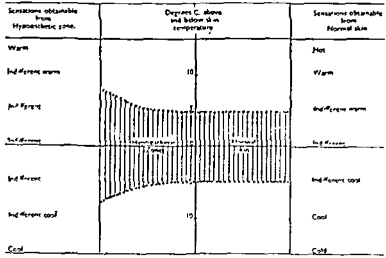


FIG. 1

Diagram representing Trotter and Davies' findings in respect of thermal sensibility.

in distribution and does not remain confined to the hypoæsthetic zone, nor fill the whole of this, but seems to be distributed over underlying subcutaneous veins. Trotter believes it to be an adventitious phenomenon and not an essential sensory result of nerve section. He points out that it does not follow the blocking of a cutaneous nerve by novocaine, and also that it differs widely in quality and distribution from the intensification of painful and cold sensations characteristic of the phase of restoration of sensory function.

In short, Trotter finds a central anæsthetic area in which the margins of total thermal, painful and tactile sensibility

correspond approximately, but not precisely. Surrounding it is a zone of hypoæsthesia, wider than Head's intermediate zone, and characterized by hypoæsthesia progressively deepening from without inwards to all modes of cutaneous sensibility. This hypoæsthesia differs in its expression according to the mode of sensibility under examination. Thus, in respect of thermal sensibility it is found that the normal indifferent zone of some 5° C. on each side of the skin temperature is widened to 10° C., and that outside this zone there is thermal sensibility, not of normal, but of diminished intensity. In respect of tactile sensibility, the threshold of stimulation—as measured by von Frey hairs—rises progressively, but once elicited the sensation of light touch is an unvarying one. Two-point discrimination undergoes the same progressive diminution as the central area is approached that is shown by other modes of sensibility. Trotter does not therefore find a specific loss of tactile sensibility or of two-point discrimination in his intermediate hypoæsthetic zone. With regard to pressure sensation, he believes that this is mainly subserved by end-organs deeper than those which subserve touch, and probably subcutaneous, but he believes that true pressure sensations may be aroused in the skin. Wherever the points of the compass (Weber's test) could be felt by pressure on the skin, some threshold was to be found. Painful sensibility also undergoes a deepening hypoæsthesia and does not show the characteristic and persistent hyperalgesia described by Head, nor is erroneous reference present. The results obtained by Head and by Trotter may be compared and contrasted, in diagrammatic form in Fig. 2.

(ii) *The Phenomena of Regeneration*

Between the tenth and fourteenth weeks after nerve section the initial signs of returning sensory function make their appearance. They are (i) the progressive and simultaneous return of tactile, painful and cold sensations, the return of true heat being apparently delayed; (ii) the development of two new phenomena not hitherto found in the area of sensory change; namely, peripheral reference

and intensification. The returning sensory functions are hypoæsthetic and full acuity is not attained for a further period of weeks. Even when the restoration of normal acuity has been reached, the two qualities of intensification and peripheral reference may persist in modified degree for indefinitely long periods.

The first sign of returning function in Trotter's seven experiments was *peripheral reference.* This differs from the

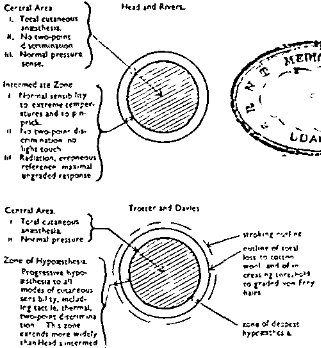


Fig. 2

Diagram comparing the findings of Head with those of Trotter and Davies.

diffuseness of response characteristic of the hypoæsthetic zone in the period immediately following nerve section, in that the sensation experienced can be minutely localized towards the distal end of the area of sensory change. It involves tactile, painful and cold stimuli, those of heat less definitely. In respect of touch the sensation actually experienced is almost identical with that evoked by light touch on normal skin, though the threshold of stimulation

is higher and when many end-organs are simultaneously excited the resulting sensation has the tingling quality of a mild faradic current. The stimulation of a cold spot gives striking peripheral reference, and painful sensations are also referred. At a later stage in the regeneration process a local reference to the spot actually stimulated may be added to the peripheral reference, and subsequently this local reference tends to increase in intensity as the peripheral reference wanes.

Closely associated with this phenomenon is that of *intensification*. This imparts an abnormally vivid quality to sensations, even though the threshold may be abnormally high: that is, intensification and hypoæsthesia may co-exist, but it tends to persist after a normal threshold has been reached, and may indeed be still present years after this has happened. It is most marked in the case of cold, least in that of true heat.

A third new phenomenon is that of *increased excitability of the regenerating nerve trunk*. The regenerating nerve trunk is found to be abnormally sensitive to stimulation, and to yield the specific sensations of touch, pain, cold and—less distinctly—of heat, when the appropriate stimuli are applied to the skin overlying it. The sensations thus evoked are referred to the nerve's area of distribution and show intensification and peripheral reference. This quality of excitability is known to obtain in the case of normal cutaneous nerves, though in a very much less marked degree than that exhibited by the regenerating portion of the divided nerve.

In considering the significance of the phenomena of intensification and peripheral reference, Trotter points out that they have no counterpart in the sensory state of the hypoæsthetic zone immediately after section and prior to the onset of regeneration. He believes that peripheral reference is due to nerve trunk stimulation and that this is incapable of yielding a local sensation, the provision of "local sign" being probably a function of the end-organ. The later appearance of local sensation is attributed to the re-establishment of connection between the end-organ and the growing nerve fibre.

Since both intensification and peripheral reference may persist after normal sensory acuity has returned, Trotter maintains that the notion of epicritic inhibition of these qualities is untenable, and that both are the product and result of damage to nervous tissue and of the resulting reaction between this and the surrounding somatic tissues.

Head lays great emphasis upon the supposed existence in the skin of the glans penis of a mode of sensibility purely protopathic in range and quality, and of an area in his own forearm possessed of exclusively epicritic sensibility. These findings he regards as confirming his hypothesis, but Trotter has little difficulty in showing that neither of these skin areas does in fact fulfil the requirements of the hypothesis, and neither allows the deductions Head has drawn.

In conclusion, it is clear that in respect both of the immediate results of nerve section and of the successive sensory states observed during the process of restoration of function, there are numerous discrepancies between the findings of Head and those of Trotter, and the essential facts relied upon by the former to prove the existence of a dual peripheral sensory mechanism, protopathic and epicritic, are not confirmed by Trotter. It is in generalizing the phenomena of sensibility to pain that the widest differences of view between Head and Trotter are to be found. For the former, pain is a purely protopathic mode of sensibility, of high threshold and non-localizable. Intensification and radiation of pain sensations are for Head essential features of this mode of sensibility, inhibited under normal conditions by the coincident activity of an epicritic system of nerves and end-organs. Throughout Head's numerous expositions, he repeatedly emphasizes the high threshold quality of painful sensibility, as, for example, "pain is always a high threshold sensation as shown by the fact that it is not evoked by punctiform stimuli until the pressure exceeds 70 gm./mm.^{2}" (H., p. 319). It is to be recalled, also, that protopathic sensibility is regarded by Head as the sole normal sensory endowment of an earlier stage in phylogenetic history of a primitive animal form.

Biologically considered, it seems improbable that a high threshold form of sensibility can ever have been normal at

any stage in evolutionary development, for it would be a quality adverse to the evolutionary process, but we do not need to invoke speculative factors of this order to see the fallacy of the conception of high threshold. By what standard is its height measured? Has this standard any biological meaning? Pain, as Trotter points out (1913, p. 138-39), has as its essential function the signalling of potential injury rather than the notification of actual damage, and pain can be elicited by stimuli below the level of intensity at which injury to the tissues is produced. In other words, the threshold for pain is below the level at which damage can be inflicted on the tissues. That it needs a von Frey hair of 7 gm./mm.^{2} to elicit it, is a fact of no physiological meaning, and not one by which we can conclude that pain is a high threshold form of sensibility. Pain serves a specific purpose for the organism; for the fulfilment of this it has a threshold appropriate to this purpose, and not high judged by standards relevant to the needs of the organism. In the electrophysiological studies of pain sensibility that we shall later consider, we find implicit in many papers the same conception of pain as a high threshold form of sensibility: either because pain fibres in nerve trunks are relatively inexcitable to electrical stimuli, or because the pain spots in the skin seem to yield on minimal stimulation a sensation of touch and only a brief sequence of nerve impulses; a greater intensity of stimulus being necessary to evoke pain and to set up the long lasting sequences of nerve impulses characteristic of pain sensations. But here also the standards of electrical or mass measurement invoked in support of this notion have no biological import. Grams and millivolts as such mean nothing to the organism. The threshold of sensibility to pain can be judged only in the light of the function pain serves in the life of the organism. So judged it is not a high threshold form of sensibility, as Trotter points out.

Conversely, to speak of tactile sensibility as of low threshold, while it is accurate in terms of gram-millimetres square of pressure from a von Frey hair, is to ignore the fact that the threshold is that appropriate to the purpose tactile sensibility serves in the organism: that of underlying

the discrimination of spatial relationships. In other words, each mode has the threshold appropriate to its function and to contrast them as "high" and "low" respectively is not to draw a biological distinction but to contrast tactile and painful sensibility in terms of physiologically irrelevant and conventional symbols.

The matter may be further considered. While tactile and thermal end-organs respond only to specific modes of stimulus, the pain endings are found to respond to a wide range of stimuli, and thus seem to lack the selective properties inherent in end-organs subserving other modes of sensibility. Thus the notion has gained ground that in some mysterious way pain sensibility is a law unto itself and does not conform to the behaviour found to govern the operation of other sensory mechanisms.

Here, again, we have to consider the purpose pain sensibility serves. If this be to signal the impending injury, the pain receptors must respond to whatever external agency threatens injury, whether this be mechanical, thermal or chemical. In other words, a pain receptor that did not respond to all forms of potentially harmful stimuli would be a receptor not adapted to its essential function, and is a structure we should not expect to find the organism endowed with. We are so accustomed to examine sensibility to pain with the point of a pin or of a needle that we have come to conclude that there is some essential biological relevance in cold steel, whereas in truth a steel point or an edge means neither more nor less to the organism than harmful degrees of heat and cold, or harmful degrees of mechanical stimulus. In short, a useful pain mechanism must respond equally to all potentially harmful stimuli from whatever kind of external agency. The one feature which does distinguish pain from other modes of sensibility is the intensity of the responses and its dominating effect on consciousness, or rather on attention ; but this also, surely, is a feature integral to a mode of sensibility possessing the purpose—if the word may be used—that all believe pain to subserve. There is nothing "primitive" about pain, as Head would have us believe, it is a highly sensitive and well-adapted form of sensibility.

In view of these considerations the fundamental differences in the interpretation of the intensification during the stage of sensory restoration that we see in Head's and Trotter's papers gain importance. For Trotter, intensification is not a phenomenon comprehended within the Jacksonian doctrine of release of function, but an essentially pathological consequence of injury to the nerve. It attaches mainly to cold and to pain. Under normal conditions thermal stimuli at both extremes tend to elicit pain rather than purely thermal sensations. Both heat and cold become burning and with the appearance of this painful element the purely thermal component in the sensation wanes and disappears. Therefore, it may be argued, a sensation of "hot" is a compound of heat and pain, of extreme "cold" one of cold and pain. Therefore in a recovering area intensification is due to the association of cold and of intensified pain. Since the sensation of true heat returns relatively late and when pain intensification is waning, intensified heat is not prominent. According to this view intensification is essentially a phenomenon attaching to pain, whether this is elicited by stimulation of end-organs or of the regenerating nerve fibre itself. Trotter attributes it to nerve fibre stimulation, and postulates an increased sensibility of the regenerating nerve fibre. This increased sensibility is in turn ascribed to the imperfect insulation of the nerve fibre and to its constant irritation by the surrounding somatic tissues of non-neural character.

Trotter's views on the insulation of the nervous system have been fully developed in other papers (1926, 1928). It is the fact that not only is the central nervous tissue completely insulated from non-neural tissues by its meninges, but the peripheral nerve fibre is equally effectively insulated by its neurilemma sheath and nowhere makes contact with non-neural tissue except in the case of the naked nerve endings in the skin which constitute the receptor end-organs for cutaneous pain. When, as after amputation, this insulation is broken down we see the extravagant proliferation of axis cylinders and the brisk reaction of non-neural tissues by which these skeins of naked axis cylinders become surrounded in the formation of the familiar amputation

neuroma. The painful phenomena of the neuroma and of the phantom limb are other indications of this incompatibility between neural and non-neural tissues, and it is to this factor that Trotter looks to account for intensification of pain sensibility during the stage of nerve fibre regeneration. The new axis cylinder is thus regarded as subjected to constant subliminal stimuli and put in a state of increased excitability. Thus, in judging between the hypotheses of Head and Trotter, we find the former invoking a purely abstract conception that takes no account of the behaviour of living tissue, the latter invoking those facts of clinical and pathological observation that, even though they be not yet provedly applicable to the problem in hand, at least accord with what we know of the reactions of living tissue to injury.

IV.—Boring's Experiment in Nerve Division

The discrepancies of observation and of theory apparent in the work we have considered led Boring to repeat upon himself the experiment in nerve division, choosing the anterior branch of the internal cutaneous nerve of the forearm ("Cutaneous Sensation after Nerve Division," *Quart. J. exp. Physiol.*, 1916, **10**, 1). Boring believed that he was better placed than his predecessors to assess alterations of cutaneous sensibility in virtue of the fact that he was a psychologist, a belief that he sets out at some length. It certainly led him to long introspective comments upon the different sensations he experienced in response to the stimuli employed: comments that sometimes leave the reader uncertain as to what precisely was experienced. Further, the branch of the nerve divided yielded a very small area of sensory change; one scarcely adequate to do justice to the psychological acumen lavished upon it. Nevertheless, Boring's observations are of interest in the light of those already discussed.

In general, he confirms Trotter's account of the sensory changes immediately produced by nerve section, and also of the successive sensory states revealed during the process of regeneration. He found a central region of cutaneous

anæsthesia surrounded by a zone of progressively deepening hypoæsthesia to all forms of cutaneous sensibility. The outer margins of this were very ill-defined and irregular. Deep sensibility to pressure and to pain remained intact, so also did one-point localization and two-point discrimination : functions that Boring regards as wholly subserved by subcutaneous pressure endings. Recovery of sensibility was uniform in rate for all modes of sensibility affected, heat being somewhat delayed. Pain, cold and heat all showed intensification and peripheral reference. One point of importance, Boring's introspections do emphasize, namely, the range of sensory qualities all commonly summed up under the term "touch." As Bazett remarks (1935), it is possible that in this regard we are letting words mislead us and that more than one sensory quality is in question here. The point is one that will be further referred to.

Boring gives reasoned arguments against the acceptance of Head's theory of a dual peripheral sensory mechanism. Some of these have already been dealt with, but there are others equally cogent that Boring brings forward. Like Trotter, he is unable to confirm Head's description of the sensory qualities of the intermediate zone, or the identity of these qualities with those displayed during the process of sensory restoration. In conclusion he assumes that a single sensory end-organ has a multiple innervation and that its stimulation leads to multiple impulses which reach the cerebral sensory mechanism there to undergo those processes of facilitation, summation and inhibition that we subsume under the term "integration." He appears to believe in the existence of inhibitory fibres, the division of which in a peripheral nerve may lead to hyperæsthesia or to abnormalities of localization.

More recently, Lanier (1935) has made some comparable experiments, using alcohol injection into cutaneous nerves as the method of physiological nerve section. Five areas of altered sensibility were produced in three subjects. He found that the area of altered sensibility to cold and warmth was more extensive than those to touch and pain, the two latter more or less approximating in extent. Signs of returning function first appeared at the end of the seventh

week after nerve blocking. Thereafter pain, cold and touch sensibility returned at the same rate, warmth being greatly delayed. No evidence of any two-stage regeneration was observed. He attributes his finding of a greater extent of thermal loss to his more adequate technique. He found a central anæsthetic area surrounded by a zone of deepening hypoæsthesia to all forms of cutaneous sensibility, including touch. He confirmed Trotter's finding in respect of the intermittent occurrence of hyperalgesia in the hypoæsthetic zone prior to the appearance of regeneration phenomena. The intensification of the stage of regeneration he compares with the "injury" effect described by Adrian. The injured regenerating nerve is supposed to set up volleys of impulses of high frequency that lead—though how, we are not told—to thalamic "over-reaction." The chief interest of these observations is their general confirmation of the facts of observation recorded by Trotter and by Boring. In short, it may be said that no observer has been able to confirm the essential facts upon which Head's hypothesis rests.

It is clear that all this work has left unsolved, even in some cases unformulated, many of the problems of cutaneous sensibility. The range of sensations rightly to be spoken of as "light touch" has not been precisely defined, and the relations of this mode of sensibility to painless pressure still remains obscure. The basis of localization and of two-point discrimination, and the rival claims made for the cutaneous and the subcutaneous end-organs respectively in subserving these capacities still await final solution. Of the varying modes of sensibility so-called, it seems probable that some at least are not rightly so described but are concepts, or judgments, based upon sensory material, *e.g.*, two-point discrimination. It has even been suggested (Bazett, 1935) that pressure sense may be a concept, due to spatial summation of numerous sublimal tactile impulses. This brings us to the nature of the stimulus subserving what we call "light touch" or "contact sensibility" (Trotter). Blake Pritchard (1931) has criticized the notion of contact as a tactile stimulus, pointing out the mechanical deformation of the tactile end-organs—the essential element in adequate

stimulation—involves more than simple contact. A degree of pressure on the skin adequate to lead to deformation of its surface is necessary to stimulate the tactile end-organ, and in this sense pressure leading to deformation is the adequate stimulus for the sensory qualities of touch and of pressure alike. The degree of pressure necessary to stimulate subcutaneous end-organs (subserving painless pressure) must, as von Frey and Strughold have pointed out (1927), involve a wider area of skin deformation than that which forms the threshold for light touch and must lead to the stimulation of cutaneous tactile end-organs over an appreciable area—possibly sublimal stimulation of many of them. Yet by the process of spatial summation a whole constellation of impulses may be set up in numerous fibres. Von Frey also records that anæsthetization of an area of skin markedly raises the threshold to deep pressure over the centre of this anæsthetic area. It seems possible, therefore, as Bazett has suggested, that the sensation we speak of as pressure derives from the activity of both cutaneous and deep sensory mechanisms, and is in the nature rather of a concept than of a primary sensation. Even light touch is not the simple matter our terminology assumes it to be. In fact, all the evidence points to the probability that we must have a physiologically sound notion of what constitutes the physiological *unit of sensory reception* before the outstanding problems of sensibility can be solved. Our pre-occupation in the past with the results of artificially stimulating single end-organs, and perhaps also our unfounded assumptions that single end-organs only were being stimulated when, in fact, a pattern of end-organs of more than one order was being excited, have led to some confusion of thought and to an undue amount of speculation.

At the time the studies under consideration were made, relatively little was known of the fundamental neural processes involved, or—apart from the description of various forms of sensory end-organ in the skin and subcutaneous tissues—of the anatomical basis of skin sensibility. Head, Trotter and Boring were therefore compelled to attempt their generalizations while lacking much of the information on these points that we now possess. It is interesting to note

what different lines of thought were pursued by them in this attempt. Head, strongly under the influence of Jackson's teachings, may be thought to have moulded his observations too ruthlessly within the framework of the abstract doctrine of release of function. Boring turned to Bernstein's speculations on central projection and diffusion to provide the integration of sensory impulses. Trotter approached the problem with a surgeon's familiarity in the handling of human tissues, and with an appreciation of the reactions which must ensue from the damage he was inflicting upon them when he divided nerves. Therefore he sought to account for some of the most striking phenomena resulting from nerve section in terms of the pathological reactions of injured tissue. This is seen in his account of the initial hyperalgesia and of the later intensification, where he expressed views that were later to be developed in his papers on the insulation of the nervous system (1924, 1926, 1928). These views have received scant attention or understanding from subsequent workers in this field, though numerous observations suggest that we may yet have to return to them. Thus, the differential behaviour of different categories of sensory nerve fibres under injuries of various kinds (pressure, nerve blocking by novocaine), and the observations of Lewis on cutaneous hyperalgesia following skin injury, all indicate that disordered patterns of sensory innervation may be the product not solely of physiological or of anatomical factors but of pathological tissue reactions.

In another respect, Trotter's more realistic attitude promises to find confirmation: namely, in his views on the nature of sensory hypoæsthesia. He expressed the view that any satisfactory theory of cutaneous sensibility must account for this phenomenon and once we abandon, as we must, Head's explanation of hypoæsthesia as the normal function of a special protopathic system of nerve fibres and end-organs, some other account of it must be provided. Trotter says: "It may be supposed that the sensitiveness of the hair bulb is dependent upon the number of nerve fibrils going to it and possibly also on their reaching it from different directions, so that the maximal neural disturbance shall be produced by movement of the hair. Suppose now the numbers of

fibrils conveying impulses away from a given hair, situated in a region where the supply of two nerves overlaps, be considerably reduced by division of one of the nerve trunks, it is clear that the normal amount of neural disturbance can only be produced by a greater movement of the hair than is usually necessary; that is to say, the hair bulb must be more firmly pressed on for a touch impulse to be originated, or in terms of sensibility the threshold of the touch spot is raised" (Trotter, 1909, p. 219). It is just such an arrangement that Weddell's recent observations have revealed, while in respect of pain Woollard has provided evidence that hypoalgesia is similarly caused. Clearly, such a generalization cannot explain the hypoæsthesia that may ensue upon lesions of the spinal cord and brain. This presents a separate problem. Yet another problem now exercising the minds of the investigators of the electrical activities of sensory nerve fibres finds its first formulation in Trotter's pages: namely, his finding of the increased excitability of the regenerating nerve fibre and of the possibility of eliciting from direct stimulation of the nerve trunk specific sensations of touch, pain and of cold and warmth when the appropriate stimuli were applied to the nerve trunk. This foreshadowed the specific activities of sensory nerve fibres subserving the different modes of sensibility that the observations of Gasser and Erlanger, and of Heinbecker, Bishop and O'Leary, to be later referred to, have revealed by other methods. In fact, the confirmation of more than one of Trotter's inferences and findings has already begun.

In brief, in view of the richly suggestive character of Trotter's writings upon cutaneous sensibility it is striking how little influence they have exerted, and the cynic might submit that this is because he coined no new words to adorn his exposition. The sway exercised upon the imaginations of neurologists and physiologists by the words "epicritic" and "protopathic" may have had not a little to do with the continued currency of the hypothesis which was their setting.

Finally, of the many investigators of the sensory changes following cutaneous nerve division only one, Pollock (1919) has drawn attention to a phenomenon of sensibility in the

area of returning nerve function that must have an important bearing upon the sensory qualities of the intermediate zone. Pollock, like Lanier, found that at the end of the seventh week after nerve division the periphery of the area of altered sensibility began to shrink at its edges and to regain sensibility to pain. This appeared at a period before regeneration was possible, and must have been due to the invasion of the denervated area of skin by nerve fibres from adjacent areas of supply. Resection of the nerve originally divided did not abolish this newly appearing pain sensibility. Thus, the sensory qualities of the area of altered sensibility, during the stage of regeneration, cannot be wholly attributed to the latter process. Recent experimental observations by Weddell, Guttmann and Guttmann (1941) confirm Pollock's surmise.

Part II

PHYSIOLOGICAL AND ANATOMICAL OBSERVATIONS

The problem unfolded by the clinical experimental studies we have been reviewing is manifestly a large one, but, as Sherrington has phrased it in another connection, " it has the interest that, large as it is, it yet—to speak *more Hibernico*—is larger still." So far, what we have been considering are gross phenomena capable of direct observation. Of the complex neural processes that underlie normal sensibility on the physiological levels they tell us very little, and while clinical studies may yet amplify and modify the facts of observation as recorded in the first part of this review, it seems unlikely that we can look to them to throw light upon the nature of much of the nervous activity involved. For this we must turn to the experimental physiologist with his command of instrumental methods of analysis and his greater choice and control of material.

The researches of Sherrington (1939) have served to define the motor unit of function, the motoneurone, and this appears to be " the motor nerve cell and the packet of

muscle fibres, 150 or more, that it innervates. It is into these packets that the reflex is found to fractionate its muscles."

So far we have heard nothing of the sensory unit of function. The studies of Head, Trotter and Boring, and of those earlier workers who identified and examined the activity of cutaneous end-organs, appear to take for granted that the single cutaneous end-organ together with its conductor is the physiological unit of sensory function. Yet if we may draw any inferences from the nervous management of movement, and the nervous system does behave consistently throughout its range of activities, it appears possible, even probable, that the sensory unit consists of all the end-organs supplied by a single posterior root fibre. If this be so, the physiological unit would be a pattern of end-organs in at least two dimensions. Further, bearing in mind that our so-called tactile sensibility under normal conditions is probably a function of combined cutaneous and deeper afferents (light touch and pressure endings), the receptor unit may be a three-dimensional apparatus of more than microscopic dimensions. It is interesting to speculate that in such an apparatus we may find the basis of local sign in sensation: a quality somewhat difficult to account for as long as we regard a single punctate sensory end-organ as the unit of function. Indeed, it would seem premature to speculate as to the basis of localization of cutaneous sensibility until we know in what the physiological unit of receptor function consists. Numerous other points equally demand elucidation: for example, whether the end-organ has a single or a multiple innervation, whether the sensory nerve fibre innervates more than one end-organ, the validity of Müller's law of specific nerve energy in the light of the most recent observations; the rôles played in the various modes of sensation by end-organs, nerve fibre, central mechanisms, by the nerve impulse and by the central excitatory states respectively. These problems call for all the resources of minute anatomy and of modern physiological methods for the analysis of sensory processes. During the past few years a great body of information has been derived from these sources, and this has made it seem probable that

the earlier studies of cutaneous sensibility discussed in the first part of this review were in some respects ill-placed to throw light upon the nature of normal sensory function, valuable as they have been in the formal description of the modes of sensory change following lesions of cutaneous nerves. They were based upon the punctate stimulation of single end-organs and upon the assumption, implicit if not explicit, that the single end-organ was the functional unit and the punctate stimulus a physiological one. By its artificial simplification, this method not only falls short of what is required, but may easily be misleading. Trotter clearly avowed his awareness of this danger.

In this field, also, we have to remember that to deduce from a study of the symptoms of lesions the normal functions of the structures injured is a complex and by no means direct problem.

V.—The Electrophysiological Study of Sensory Function

The assessment of the results of modern electrophysiological methods is not easy for the clinical neurologist. This field of work is a highly specialized one which he will enter with diffidence and tread with circumspection, yet ready to view critically the large claims that are so apt to be made by enthusiastic exponents of new methods. Nevertheless, if it be true, as Boileau hopefully expressed it, that "ce que l'on conçoit bien, s'enonce clairement," he may hope to gain some light from the study of recorded observations, and he may even in virtue of his familiarity with other lines of attack upon the problems of sensory function, have a peculiar advantage in applying the fruits of special methods to their elucidation.

The foundation of this line of approach consists in the analysis of the nerve impulse: that is, its excitation by stimulation of receptor organs or of the nerve fibre itself: its potential value, its characteristic frequencies, and the modifications imposed upon it by the nerve channels in which it runs. This analysis has been made possible by instruments which not only register the potential change that

constitutes the nerve impulse, but also amplify it sufficiently for its recording and measurement. The earlier workers (Keith Lucas, Adrian) employed the capillary electrometer. Later the moving iron oscillograph of Matthews and the inertia-free cathode ray oscillograph (Forbes, Gasser) were devised and, employed with vacuum tube amplifiers of increasing power, have revealed in end-organ and nerve fibre electrical phenomena not earlier discernible. In the monographs of Adrian (1928, 1935) and of Erlanger and Gasser (1937), the reader who is interested will find descriptions of these various forms of apparatus.

The original studies of the properties of end-organs and of nerve fibres were carried out by Adrian and his co-workers (Adrian and Bronk, Adrian, Cattell and Hoagland, Adrian and Zotterman). Later, Gasser and Erlanger and others took up the analysis of the compound potential changes in nerve trunks, determining the various fibre components involved and relating them to specific sensory activities.

Whether studied in an afferent or an efferent nerve, the individual nerve impulse is a remarkably constant and unvarying phenomenon. While impulses may vary in their potential value and their conduction rate, and in the sequences in which they occur, they display throughout the entire range of nerve fibre activities no qualitative differences, so that the notion of nerve impulses of specific character finds no support.

The conduction of the nerve impulse is the essential function of the nerve fibre. The impulse consists in a wave of electronegativity that passes along the fibre, leaving in its wake a transient phase of refractory state during which no further impulse can follow. Any prolonged activity of the nerve fibre is therefore necessarily rhythmic, the maximal frequency of nerve impulses being determined by the duration of the refractory state.

The stimulus, whether it arises in a sensory end-organ or from the direct stimulation of the nerve fibre, acts by setting up in the fibre a local and non-propagated excitatory state. When this reaches a certain threshold value—peculiar to the fibre in question—an impulse is set up and is, for that fibre, of constant and unvarying value (potential). This is

expressed in the statement that there is an "all-or-none" relation between the stimulus and the propagated activity it excites in the nerve.

Whatever we understand by Müller's law of specific nerve energy, it does not apply to the simple nerve impulse as such, for this is found to possess no specific qualities. Whether set up by end-organ or nerve fibre stimulation, and whether subserving motor or sensory function, it does not vary in essentials. Therefore, when Head states, as we have seen, that "each impulse is stamped with the characteristics peculiar to the organ in which it has arisen," the notion—essential to his theory—is seen to be untenable.

Yet, while the exciting stimulus cannot grade the intensity or influence the essential character of the impulse, it can determine the total activity of the nerve fibre by controlling the number and frequency of impulses set up, subject always to the limitations imposed upon the nerve fibre by its refractory state and by its rate of adaptation.

The essence of a stimulus adequate to set up nerve impulses is that it should produce a local change in the nerve of sufficient gradient, and a stimulus of progressively increasing strength is more potent than a constant stimulus. Thus direct stimulation of the nerve fibre by a stimulus of constant strength rarely sets up more than a single impulse, for the fibre rapidly becomes adapted, the stimulus falls below threshold value in consequence, so that by the time that the refractory phase following the initial impulse has passed off it has become inadequate.

A somewhat different state of affairs is revealed by Adrian's studies (1928) of the sensory end-organs in skin, subcutaneous and muscular tissues. When the nerve fibre is stimulated physiologically through these normal channels a sequence or volley of impulses is commonly set up in the nerve fibre.

A considerable number of different types of sensory end-organ in skin and deeper somatic tissues has been described. Some of these have been identified as subserving specific sensory functions, but the precise sensory correlations of many of them remain undiscovered, or at most but the subject of surmise. At the present juncture all that we have

to consider are the general qualities exhibited by sensory end-organs. In the matter of adequate stimulus we have a group (tactile, pressure and postural) for which the stimulus is mechanical deformation, and this probably acts by stretching the terminal part of the sensory nerve fibre within the end-organ. Another group, heat and cold spots, respond to *exchanges of heat at the body surface: the heat spots to* additions, the cold spots to subtractions of heat, and not to temperature scale variations as such. A third group, of which the pain receptors are the striking example, respond to example, respond to mechanical, chemical and thermal stimuli. The purpose of this wide range of response on the part of the pain end-organs has already been discussed. *Thus, four primary modes of cutaneous sensibility are* generally believed to occur: touch, warmth and cold and pain. Closely associated with these are deep pressure and pressure pain: functions of subcutaneous end-organs.

Attaching to sensory end-organs of all forms are qualities which suggest that we may regard them as modified nerve fibres. They can be made to give frequencies of discharge *up to the limiting capacity of the nerve fibre. Their rapidity* of adaptation to stimulus varies from type to type, being rapid in tactile receptors, less so in the postural (muscle spindle) receptors. These qualities are so graded that the nerve fibre cannot be pushed beyond its capacity: that is, the fibre can carry impulses of a frequency as rapid as the end-organ can evoke in it. Similarly, the slower rate of adaptation of the end-organ allows it to set up sequences of impulses. The muscle spindle which is responsive to stretch of muscle is so slowly adapting that it sets up sequences of impulses of relatively long duration, while the rapidly adapting tactile end-organ may upon minimal stimulation *adapt so rapidly that only a single impulse is set up. Adrian,* Cattell and Hoagland (1931) made a skin-nerve preparation in the frog containing but a single sensory nerve fibre, supplying tactile end-organs to a relatively wide area of skin. They found these end-organs to be rapidly adapting, impulses being set up only during the actual movement of the skin. Repeated skin stimulation (by an intermittent air blast) set up impulses of high frequency and long duration,

the frequency reaching a rate of 200 per second. The last-named mode of stimulation gave rise to none of the reactions commonly associated with pain, and it seems, therefore, that the end-organs excited by this mode of stimulation are specific for light touch and do not subserve pain. Another point of interest is that, as the sensory nerve fibre branches distally to supply several end-organs, so stimulation of a single receptor sets up impulses not only in its own conducting fibre, but also impulses of identical frequency and character that pass distally (antidromically) down the other branches of the parent nerve fibre to influence the activity of end-organs not themselves subject to stimulation. The fibres concerned appear to belong to the β fibres in Gasser and Erlanger's "A" group of large myelinated fibres, to which reference will be made. In a subsequent investigation, Cattell and Hoagland (1931), on the same type of material, found the tactile end-organs rapidly adapting, and found the end-organs that are antidromically reached by impulses have their excitability reduced. This important finding suggests that the physiological unit of sensory function—or of sensory reception—comprises all the end-organs innervated by the branches of a single posterior root fibre: the stimulation of any one leading to the modification of the activities of every other. That is, the unit appears to be a skin area that—even in the frog—may cover 100 sq. mm.

The end-organs subserving pressure are less rapidly adapting than those subserving purely tactile sensibility, and with a steadily increasing pressure on the skin set up in the nerve fibre a sequence of impulses of waxing and waning frequency. The central responses to light touch and to pressure also differ, in that light touch remains a discontinuous, or intermittent, sensation however rapid the frequency of stimuli, while pressure is a continuous sensation.

The impulse response to stimulation of pain endings in the skin shows characteristic features. To a penetrating pin-prick the initial sensation is one of painless touch and this is accompanied by a brief outburst of impulses. As penetration goes deeper, the impulses resume—or continue—at their original amplitude but with increased frequency, and a long after-discharge of impulses follows the cessation of stimulation.

The initial sensation of light touch that ensues upon minimal degrees of pin-prick has led to the suggestion that pain receptors serve both a tactile and pain function. The weight of evidence seems against such an assumption and in favour of the specificity of the pain end-organs, for in areas of skin containing nothing but pain fibres and their endings (Woollard, Weddell and Harpman, 1940) this initial sensation of touch is not felt. When present, therefore, it may be due to the concomitant stimulation of tactile endings. Further, the persisting quality of the pain of injury has led Adrian (1935) to suggest that the rapidly adapting mechanism that subserves pricking pain cannot also subserve the persisting pain of injury. Further reference to this point may be deferred till we come to consider Woollard's work. In the meantime, we may emphasize again, as in the opening pages of this review, the fallacies latent *in the tendency to postulate multiple peripheral mechanisms* to account for obscure aspects of sensory function.

Other observations of Adrian suggest that the volley of impulses that traverse the length of a nerve fibre have imprinted upon them features dependent upon the anatomical characters of the fibre. For example, in many instances the impulses subserving pain are of small potential and slow rate of conduction, suggesting their carriage in small fibres. Ranson (1931, 1935) believes that the small unmyelinated fibres of the posterior root that enter Lissauer's tract in the cord subserve pain, and with Billingsley (1916) found that stimulation of these fibres in the experimental animal yielded reactions indicative of pain. Woollard's work also indicates that small unmyelinated fibres may play a part in pain conduction.

These observations lead us to ask whether variations in fibre size, in amplitude of potential and in rate of conduction have significance in the study of sensory function, and we are thus brought to the second phase in the electrical analysis of nervous sensory activity: that undertaken by Gasser and Erlanger (1937) and by Heinbecker, Bishop and O'Leary (1933, 1934, 1935) who have investigated what is known as the compound action potential by means of the cathode ray oscillograph.

Gasser and Erlanger find that if the sciatic nerve of the bull frog be stimulated electrically at an increasing intensity, all the component fibres of the nerve are finally thrown into activity. These fibres show different grades of excitability, differences in the amplitude of their potentials, and differences in their conduction rates; that is to say, as the stimulus gains in intensity, fibre after fibre fires off a sequence of impulses. This summed activity is reflected in the compound potential record. By the study of the record, it has proved possible to analyse the fibre composition of the nerve and to classify the fibres into types. Inferences have also been drawn as to the functional significance of the types thus differentiated. In comparable studies Heinbecker, Bishop and O'Leary have confirmed these observations on mammalian and human material, though they adopt a somewhat different nomenclature and basis of fibre classification.

To understand this work it is necessary to depict diagrammatically the compound potential and to name its component elements.

The compound potential shows three main waves, A, B and C. The A wave is the largest and most rapid and has three components α, β and γ. The B wave is smaller and of longer duration, and after an interval is seen a long drawn-out wave C. Electrical analysis and histological control reveal that the fibres responsible for the A wave are the largest in diameter and the most rapidly conducting, and from the place they occupy in the record must have the lowest threshold of excitability. At the other extreme are the small, least excitable and most slowly conducting fibres. The fibres producing the B wave are intermediate in these qualities (Fig. 3).

The functional correlations of these three main fibre groups have been determined by different methods: namely, (i) by the correlation of fibre size with the distribution of nerve endings in the relevant area of skin; (ii) by the comparative response to nerve blocking as judged by potentials and by sensory responses in the human subject; (iii) by the measurement of conduction rates of the impulses set up by stimuli exciting different modes of end-organ; and

(iv) by the determination of the sensory qualities of the responses to stimuli graded to excite different components of the nerve. From these various studies the present state of opinion appears to be as follows: To cocaine blocking of the nerve, the fibres go out of function progressively in the inverse order of size, C, B and A. On the sensory side the different modes go out in this sequence: cold, warmth, pain and pressure, or according to other observers: pain,

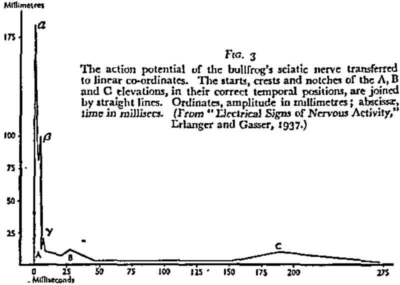


Fig. 3
The action potential of the bullfrog's sciatic nerve transferred to linear co-ordinates. The starts, crests and notches of the A, B and C elevations, in their correct temporal positions, are joined by straight lines. Ordinates, amplitude in millimetres; abscissæ, time in millisecs. (From "Electrical Signs of Nervous Activity," Erlanger and Gasser, 1937.)

cold, warmth and pressure. The fibres subserving pressure are the largest of the sensory components of the nerve, those subserving postural sensibility being of much the same order. It seems that afferent fibres stimulated by mechanical deformation of their end-organs (touch, pressure and posture) are widely distributed through the A range. They are the last to be blocked by cocaine. Vibration sense goes before light touch, then pressure follows, and it seems likely that both the former are subserved by fibres of a larger average diameter than those subserving pressure. Warmth and pain are subserved by fibres slightly larger than those for cold, but also by the smallest C fibres. Pain is served by a wide range of fibre sizes, and some pain (delayed pain)

is conducted by the C fibres, which remain active when all other fibres have been blocked. Cold is subserved by the narrowest range of fibre sizes. On the whole the fibres associated with each different modality of sensation are widely distributed through the fibre range, and the evidence so far as it goes tends to support the view that sensory fibres are grouped according to function and are specific. The fastest fibres are those that respond to mechanical deformation of their end-organs, those responding to thermal and other modes of stimulation being slower and smaller. Little is yet known of sensory fibres of the second physiological level in the cord, but it seems that conduction rate in the sensory path at the level of the posterior column nuclei is only one-third that at the level of the posterior roots, and the fibres at the former level are smaller than the peripheral sensory neurone. It may be added in conclusion that present interpretations of these various electrical and other analyses of sensory fibre function have not reached finality. Some of the most recent potential analyses are of a highly complex character, and have attempted to determine the afferent fibre systems subserving tickle and itching (Zotterman, 1939). The steps of these analyses are far too complex and employ a special terminology too recondite for their assessment by the clinician, and an impression is aroused that possibly too much is being asked of the method in elucidating physiological function at its present stage of development. Yet with a method already so fruitful and so steadily advancing in delicacy it would be premature to say that it will not provide an even greater harvest before its resources are exhausted.

In short, all these investigations still support the old idea that there are four primary sensory modes—touch, pain, cold and warmth, and probably also subcutaneous pressure and pressure pain modes. They have shown conclusively that the individual nerve impulse is not of primary importance in the determination of the final sensory effect, but that the sensory pathway *as a whole* has components specific for each mode of sensibility. Each component in the pathway contributes an element to this specificity: the end-organ with its selective excitability and adaptability

(factors that vary with each sensory mode) determines the mode of activity of the conducting nerve fibre (the frequency and duration of the volleys of impulses); the fibre itself in virtue of its size (which conditions its excitability and conduction rate) also imprints specific effects upon the impulses that traverse it; while, finally, the central destination of each specific sensory group of fibres, and the variations in the central excitatory states, act as the final determinants of the sensory effects. There is, therefore, a mode of specific nerve energy, not resident in the single impulse, but a product of the combined activity and morphology of each component of the sensory path. In this way the four primary modes of cutaneous sensibility, combined with the sensory impulses received from deep somatic structures, afford support for the view that all the complex sensations experienced can be adequately accounted for as a central integration or fusion of simpler primary ones. The number of variables that exist, physiological as well as anatomical, the permutations and combinations of impulse frequency, duration and intensity, the number of fibres in action and the interaction of cerebral mechanisms offer an adequate basis for a wide range of sensory experiences derived from a few specific components. As Jackson pointed out, a few muscles can be combined in different ways to perform an almost infinite variety of movements just as the few notes of the octave can be combined and changed to produce an infinite variety of tunes. Probably, then, the central mechanisms that subserve sensation on the physiological level can serve with equal efficiency to provide the whole range of sensory experience from the material provided by the mechanisms we have reviewed.

One other point of interest in the experiments of Heinbecker, Bishop and O'Leary (1934) may be mentioned in connection with an observation of Trotter's already referred to. Trotter found that in response to tactile, painful and thermal modes of stimulus the regenerating cutaneous nerve trunk responded by yielding all the appropriate modes of sensation, thus revealing specific sensory qualities in nerve fibres when excited in the absence of their specific end-organs. This finding is in harmony with what electrical analysis has

revealed of sensory nerve fibres, but, in addition, the observers named find that direct electrical stimulation of an exposed human cutaneous nerve yields sensations of touch and pain, thermal modes of sensation not being elicited by this form of stimulus.

Throughout the observations thus summarily considered, the notion is implicit that local sign is not so much a function of the individual end-organ, as of the interaction of impulses of varying frequency and intensity derived from the simultaneous and successive activity of numerous end-organs, working perhaps in patterns. Indeed, it seems that the important lesson to be learned is that we must not think of the individual end-organ and its fibre as the physiological unit of sensation.

So far, no direct study of the identity of *the physiological unit of sensory function* has been discussed, though, as we have seen, Cattell and Hoagland's observations throw light upon the matter. The problem has recently been attacked by an ingenious method by Sarah Tower (1940). She asks: " What is to be considered the unit nerve ending: all the terminal tissue of one nerve fibre or the separately encapsulated portions of terminal tissue? " In the case of the rich formation of unencapsulated nerve endings in the skin that subserve cutaneous pain, the product of free branching of sensory nerve fibres, the question seems still more to call for an answer. In the frog's skin Adrian, Cattell and Hoagland (1931) found that appreciable areas of skin were innervated by the branchings of a single neurone. Tower (1935) found that in the frog's viscera a single afferent fibre may innervate an area of from 2 to 3 sq. mm. Her present investigation takes the rabbit cornea for its sensory field. The terminal ramifications of a single afferent fibre comprise a unit area of from 50 to 200 sq. mm., the area having sharply defined limits. If we regard these branches and the fibre from which they arise as a physiological receptor unit we have something remarkably like the motor unit already referred to. Activity anywhere within this unit area is found to influence the whole, but not to influence adjacent sensory units in the cornea. Adaptation and fatigue phenomena were confined to the unit, and an impulse

generated in one point of the unit area appeared to spread throughout the area to alter excitability at other regions within it. Tower therefore concludes that " the sensory receptor in the cornea emerges as all the terminal tissue of one nerve fibre. This is a unit, activity in any part of which affects the whole . . . the corneal sensory mechanism appears as an aggregate of units and not as a continuum.

While it is clear that much evidence remains to be gathered, it seems highly probable that this finding expresses a state of affairs that obtains throughout the sensory receptive mechanism. The anatomical studies of Woollard all point in this direction. Before closing this brief summary, mention should be made of another series of investigations which bear upon the central destination of the pathway for tactile sensibility. Marshall, Woolsey and Bard (1937) explored the monkey's cortex to see if tactile stimulation of the skin evoked in any part of it electrical changes that might be considered to indicate the arrival of the relevant impulses, and to localize the situation of the sensory cortex. Bard (1938) has summarized their findings as follows: the application of discrete tactile stimuli to any cutaneous area evokes in a well-defined cortical area well-localized potentials, and reveals a detailed topographical representation of the body surface in Brodmann's areas 3, 1 and 2 that follows the same general plan as the similar cortical representation of movements in the precentral convolution. This sensory representation is strictly crossed. They consider it probable that the cortical area thus revealed is the projection area of the thalamocortical fibres subserving tactile sensibility, and the potentials may represent the summed action potentials of these fibres.

VI.—The Anatomy of Cutaneous Sensibility

The punctate nature of cutaneous sensory end-organs has long been established on a sound anatomical and physiological basis, but while the various types of these receptor organs have been minutely described by histologists, the mode and pattern of their innervation has remained largely unknown. Yet a full understanding of their contribution to sensory

function requires that we shall know the nature of their nervous connections. Within the past few years by the adaptation of the method of staining nerve fibres *in vivo* by methylene blue, Woollard and his collaborators and successors in this work have added greatly to our knowledge of the nervous structures present in the skin, and have clarified much that was obscure. These most fruitful researches initiated by Woollard before his premature and regretted death have been pursued by Weddell and others, and promise to resolve many of the outstanding problems in the anatomy and physiology of cutaneous sensibility. In truth it is clear that the anatomist must have the last word in this long search to reveal the sensory functions of the body surface, for where there is no structure there can be no function. At least two of the hypotheses considered in this review must be regarded as wanting in validity because the postulated foundation of structure upon which they are built has been found, by these investigations, to have no existence.

By a series of comparative histological studies, using vital methylene blue staining, in the dog, fish, rabbit, monkey and man, it has been found that there is a remarkably constant pattern of sensory innervation in the skin. This is most complex in the monkey and man in respect of the variety of end-organs present, but throughout the series the general architecture is strikingly alike.

Deep to the skin sensory, nerve bundles are found which branch freely, sending ramifications in all directions to enter the skin. Therein they form two main nerve plexuses, deep and superficial. Thick and thin nerve fibres, both medullated and non-medullated, compose these plexuses, the deeper being on the whole composed of fibres of greater diameter. Within both plexuses fibres of varying calibre may be seen to run inside a single neurilemma sheath. In the skin of the rabbit's, ear thick fibres are seen to innervate hair follicles. Each follicle may contain as many as ten hairs, and as many as seven terminal fibres may innervate a single follicle. The ramifications of a single fibre may innervate as many as 300 follicles (Weddell, 1941 (*c*)). Further, each follicle receives a dual principal innervation,

receiving a main fibre from at least two parent stems. In addition to this hair follicle innervation, finer fibres from the superficial plexus are seen to shed their medullary sheaths, to become varicose and to branch repeatedly to form rich arborizations of naked and beaded terminals which lie below and between the epidermal cells.

In human skin the same deep and superficial plexuses are to be seen. The finer branches enter the stratum mucosum and stratum granulosum and, branching freely, provide the rich network of beaded terminals already described. Further, fine non-medullated fibres are seen to provide an "accessory" innervation to complex end-organs of various types in the skin, *e.g.*, to Meissner's corpuscles and to Krause end-bulbs. These accessory fibres expand and form a skein in the end-organ. Thus each group of these end-organs receives a dual principal innervation and an accessory innervation (Weddell, 1941 (*b*)).

The fine branchings which arise from the superficial plexus form a prominent feature in the skin. The branches from each parent fibre interlock with those from other fibres, but there is no continuity between overlapping arborizations. These fibres and those providing the accessory innervations are of the same morphological type, and for reasons to be considered, it is concluded that they constitute the anatomical mechanism of cutaneous pain sensibility. The arborizations arising from different parent fibres each innervate a roughly circular area of skin, of dimensions that vary from one body region to another. Thus, on the dorsum of the hand such a single area may have a diameter of no less than 0·75 cm.

The Meissner's corpuscles, which are thought to subserve tactile sensibility, are most thickly sown in the papillæ of the skin of the finger tips, 1 sq. mm. containing as many as ten groups of two or three corpuscles. These organs are commonly thus grouped and are rarely solitary. A "touch spot" as known to the physiologist consists of one or more groups of the corpuscles, and it is found that at least two main fibres, relatively thick and medullated, innervate each "spot." In addition, each corpuscle has its fine "accessory" fibre. Krause end-bulbs, believed to subserve the sensation

of cold, are similarly grouped and innervated, and it seems probable that a " cold spot " comprises one or more small groups of these endings, with a dual principal innervation and an accessory fibre to each end-bulb. Another form of end-organ, Merkel's disc, has been observed in the skin of the monkey's thumb.

It will be appreciated that this arrangement of end-organs in groups and in particular the groupings of naked nerve-endings in area and in depth, is that outlined by Trotter as governing the innervation of the skin. It provides an explanation of sensory hypoæsthesia, since immediately after section of a cutaneous nerve a given group of end-organs has less than its full innervation. During regeneration the full multiple innervation is only gradually restored. Thus stimulation of a given " spot " tends to set up less than the normal amount of neutral disturbance. In respect of the free endings, the diminished number of endings and the absence of overlap has a comparable result in respect of painful sensibility. By novocaine blocking, in succession, of two cutaneous nerves innervating adjacent areas of skin. Woollard, Weddell and Harpman (1940) found that the contiguous margins of tractile insensibility coincide, but that there is a gap of about 1 cm. in width between the adjacent margins of analgesia to pin-prick. In other words, as Head had found, the distribution of the pain fibres in a given nerve is more extensive than that of fibres subserving tactile sensibility. In this gap of 1 cm. width fibres and endings subserving pain overlap, and this narrow zone receives its pain fibres from two adjacent nerves. When, in this zone of overlap, one nerve is divided, the number of pain spots is found to be reduced and the threshold of pain sensibility raised. Weddell, Guttmann and Guttmann (1941) find evidence of similar overlap in the rabbit. For a given cutaneous nerve they find a central " autonomous " area supplied by the divided nerve alone, an " intermediate " zone of overlap, and a maximal zone—comprising both the preceding—that constitutes the entire area of distribution of the nerve.

They also find that, shortly after nerve division, the intermediate zone begins to shrink peripherally, and find

histologically that the reason for this shrinkage is the invasion of the partially denervated skin by advancing pain fibres from adjacent intact nerves. In other words, the early stages of apparent restoration of pain sensibility are due, not *to regeneration of divided fibres*, but to growth of nerve fibres subserving pain in adjacent areas. As already mentioned, Pollock found a similar state of affairs in the human subject.

Another feature of cutaneous innervation revealed by all these observations is the dispersal in all directions of the nerve fibres that enter the skin. In this way they approach the region they are to innervate from widely different directions. Thus the fibre that finally reaches the centre of a given area may have further to travel than one that innervates its periphery. Hence, during the process of regeneration, the growing fibres have different distances to travel and cannot simultaneously re-form their former connections with their appropriate end-organs.

In addition to these histological investigations, Woollard and his co-workers (Woollard, Weddell and Harpman, 1940; Weddell, 1941 (*a*), 1941 (*b*), 1941 (*c*); Weddell and Glees, 1941; and Weddell, Guttmann and Guttmann, 1941) have carried out a number of physiological observations directed to the study of cutaneous pain sensibility.

It is found that the penetration of the skin by sharp needles may yield sensations of touch, pressure, cold, warmth, and pain, or—upon occasion—no sensation. Penetration of the skin is essential to the production of pain, and like many earlier observers they find the pain to be of two qualities.

Thus, there is (i) an abrupt, brief, painful sensation that hurts relatively little, followed as penetration proceeds by (ii) a delayed pain of increasing intensity, like a small stinging area, and of slow waning. It may not reach its maximum for two seconds. The two pains may follow without an interval (phasic pain sensation) or an interval may separate them, this feature varying according to the body region stimulated. In respect of the different modes of sensation yielded by a prick, they note that the "first" pain is elicited on a penetration of 0·25 mm., "second" pain at 1 mm., cold at 1 to 1·5 mm., warmth at 1·75 to 2·5 mm., pressure

at 2 to 2·5 mm., and—paradoxically—touch at 2 mm. penetration. This last result is not so odd as might at first sight appear, for an extremely sharp-pointed needle may well penetrate relatively deeply before causing that deformation of the surface of the skin that is the essential condition of the stimulation of a touch corpuscle: a consideration that deprives the argument that pain receptors may also subserve tactile sensibility of its force.

Further investigations showed that in areas of skin which subsequent examination revealed as containing only the free nerve endings already described, the only sensation yielded was pain. Both "first" and "second" pain were localized with equal accuracy, and the discrimination of two successive pricks was achieved with accuracy when sufficiently far apart (1 cm.) to include the areas innervated by the branchings of two adjacent parent fibres: that is to say, when they were so placed as to set up separate impulses in two afferent fibres. Since, as we have seen, the pain mechanism is disposed in depth as well as in area with pain fibres lying in both deep and superficial plexuses (the final branchings arising from the latter), Woollard believes that both superficial and deep pain are subserved by a single neural mechanism. Deep pricks pass through the disposition of the mechanism in depth and stimulate not only superficial arborizations but also deep nerve fibre handles. He thus accounts for the greater intensity and diffuse character of deep pain on the basis of spatial summation.

Finally, pain appears to be subserved wholly and exclusively by terminal nerve twigs with free nerve endings, and he finds no trace of any other such arrangement of fibres in the skin, thus invalidating the hypothesis, to be later discussed, that there is a separate "nocifensor" system of cutaneous nerves of this morphological type.

We see, therefore, that the unit of pain reception appears to be, not a single pain spot, but all the branchings and free endings of a single parent fibre, disposed in area and in depth, and of a total volume of macroscopic dimensions. From what Tower has shown of the widespread activity within such a unit when one point of it is stimulated, we may probably find in this arrangement the basis of local sign in

painful sensation. The more highly organized end-organs subserving other modes of sensibility: tactile (Meissner's corpuscles, Merkel's discs), cold (Krause's end-bulbs), warmth (Ruffini's endings), pressure (Golgi-Mazzoni and *Ruffini endings) appear, as far as can be ascertained, to* be arranged on a similar plan, and thus it seems probable that localization is achieved in respect of each modality in virtue of the massed arrangement of the individual end-organs and of the multiple innervation of each group of these organs.

A further word remains to be said of the "accessory" fibres seen in different types of cutaneous end-organ. Morphologically these resemble the fibres subserving pain, and Woollard suggests that they may by their presence there signal the advent of supramaximal and potentially harmful stimuli; that is, they may act as a form of "burglar alarm" in the ending. Their presence might also account for the wide range of stimuli that is capable of yielding a sensation of pain: a notion compatible with the specific activity of each type of end-organ.

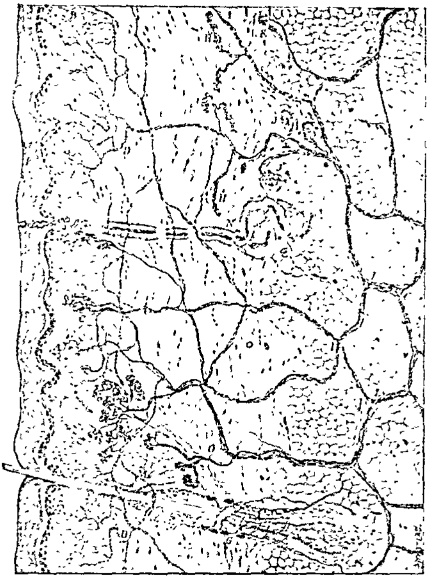
Fig. 4, taken from the paper by Woollard, Weddell and Harpman (1940), represents the authors' conception of the innervation of the skin as seen in section.

Weddell and Harpman (1940) have also studied the sensory end-organs in deep fascia, periosteum and tendons, and their findings have some relevance to the problem of pain sensibility. They find three types of nerve ending in these structures: a freely branching system of fine fibres terminating in free endings, Vater-Pacini and Golgi-Mazzoni endings. Each of the two last receives the same fine "accessory" fibre that has been described in Meissner's and Krause's end-organs.

Part III

SOME CONCLUSIONS

In a passage cited earlier, Head remarks that "between the impact of a physical stimulus on the peripheral end-



From the "Journal of Anatomy," by courtesy of The University Press, Cambridge

Fig. 4

Composite diagram showing the innervation of the human skin. *A*, Merkel's discs, subserving touch. *B*, Free endings, subserving pain. *C*, Meissner's corpuscles, subserving touch. *D*, Nerve fibres, subserving pain. *E*, Krause's end bulbs, subserving cold. *F*, Nerve-endings, subserving warmth (sometimes called Ruffini's endings). *G*, Nerve fibres and endings on hair follicle, subserving touch. *H*, Ruffini's endings, subserving pressure. *I*, Sympathetic nerve fibres innervating sweat glands. *J*, Pacinian corpuscles, subserving pressure. *K*, Golgi-Mazzoni endings, subserving pressure. *L*, Nerve trunks containing thick and thin fibres. *M*, Sebaceous gland. *N*, Sweat gland. *O*, Sympathetic fibres supplying arrector pili muscle. Drawing composed from methylene-blue and reduced silver preparations. The functional interpretations above are based upon observations by the writers. (From Woollard, Weddell and Harpman, *J. Anat.*, 1940, 74, 427.)

organs of the nervous system, and the simplest changes it evokes in consciousness, lie the various levels of physiological activity . . . by the time afferent impulses reach one of those centres where they can form the underlying basis of sensation they have been profoundly modified." Yet from what has been said, it seems clear that the physiological processes concerned are not what Head envisaged. Until the highest centres of sensory function are reached, the impulses subserving the four primary modes of cutaneous sensibility appear to travel virtually unchanged, and do not undergo the remarkable modifications in spinal cord or brain-stem outlined by Head. It appears likely from what we have recently learned of the innervation and grouping of sensory end-organs that the impulses in virtue of their multiple source in double innervated end-organs, and of their different frequencies and sequences, provide much more complex sensory material for integration than Head supposed, or could have known. It seems likely, for example, that local sign in sensation is subserved by the spatially and temporally dispersed origin of impulse volleys.

Of the further central modifications that sensory impulses undergo very little is known, though something can be surmised if we turn to the great deal that is known of the central nervous management of movement. The student of sensory functions most deeply versed in the work of Sherrington and his school is probably he who will see furthest into the physiological problems of sensation. In this connection it may be suggested that no student of these problems can afford to neglect the article on cutaneous sensation written in 1900 by Sherrington in Schafer's two-volume textbook of physiology. The workers on cutaneous sensibility of the closing years of the last century saw deeply into the problems involved in tactile localization and discrimination, and their observations are only to be found assembled and critically examined in Sherrington's article. We may yet have to go back in thought to this relatively remote period in physiological history, and consider sensory functions in the light of what was then thought, and what is now known, before success rewards our efforts in this most complex of problems.

VII.—Problems of Cutaneous Pain Sensibility: The Nocifensor System

No mode of cutaneous sensibility has been the subject of so much speculation and of such conflict of opinion as cutaneous pain. It has been spoken of as being of high threshold, as possessing receptors responsive to a wide range of stimuli, mechanical, thermal and chemical; as being subserved by two separate peripheral mechanisms—the one responsible for the brief rapidly developing pain of a prick, the other for the more slowly developing and longer lasting pain of injury; slow and fast pain fibres have been postulated each subserving different modalities of pain; according to Head the peripheral mechanism concerned is of "crude" function and "primitive" phylogenetic history, capable of eliciting maximal and ungraded sensations and endowed with no precise local sign; Trotter has emphasized the disproportion between stimulus and the overwhelming nature of the sensation resulting in consciousness; while the function of pain as protective, or as signalling impending injury to the tissues, has been widely accepted. In the field of electrophysiology comparable variations in view have been expressed.

There are, as Trotter has pointed out, limitations to the notion that pain serves a primarily nociceptive or protective function. Thus, to the lethal X-ray it yields no response, while some internal maladies of fatal issue are advanced beyond hope of treatment before they elicit any activity in the mechanism subserving pain. Yet in respect of trauma—and we are now considering *cutaneous* pain sensibility—it seems reasonable to agree that pain does signal impending external injury and thus serve a protective function. Again, as Trotter has emphasized, the stimuli adequate to elicit pain are of a quality less than necessary to injure the tissues, and so, if we accept the protective function of pain, we cannot reasonably speak of it as a high threshold mode of sensibility. The mathematical and mechanical standards by which in the past we have tried to calibrate the threshold value of the pain receptors are, as has been suggested, wholly irrelevant to the organism. Further, the sensitivity of the cutaneous pain receptors to

a wide range of stimuli is not a quality that, biologically considered, differentiates them from those subserving other modes of sensibility. This mechanism responds to potential noxa. We have agreed that it is its function to do so, and in this sense the response is not less specific than those of other receptors. Here, again, we have to consider the biological relevance of different forms of adequate stimulus.

That these receptors also subserve tactile sensibility is a notion that we have seen to contain a fallacy, since in areas of skin deprived of tactile sensibility and containing only the specific endings for pain, no touch is felt. The penetration of the normal skin by a pin when it is progressive must sooner or later—and this according to the fineness or otherwise of the extremity of the pin or needle—deform the skin and thus stimulate both tactile and pressure nerve-endings.

Woollard's observations lend no support to the view that there are two peripheral mechanisms for pain. The wide area and appreciable depth of skin supplied by the arborizations of a single sensory parent fibre make it clear that a penetration of any depth by a sharp needle must " touch off " a number of pain nerve-endings and nerve fibre bundles. In the case of any given single stimulus of this order, no one can ever say within wide limits what amount of neural disturbance has been set up, that is, how many volleys of impulses in how many fibres have been excited. This point of view receives some confirmation when we consider what happens in an area deprived of overlap by the section of one of the two main nerves supplying an area of skin. The pain endings and fibres are found to be less numerous and the threshold raised. The hypoæsthesia is a natural result of the stimulation of fewer receptors.

A somewhat different problem—at least on a superficial view—is provided by the persistent hyperalgesia that follows minor damage to the skin. There are several indications as to how this may arise, but the most elaborate hypothesis is that advanced by Lewis (1936) who has postulated the existence of a special system of nerves which, acting in association with the pain nerve-endings, specifically subserves this sensory reaction. This he names the "nocifensor system."

Like Head's hypothesis, this one seeks to generalize clinical observations by supposing the existence of an ana-

tomical mechanism of which no direct evidence is provided. In the course of observations carried out with Hess (1933), Lewis noted the development of cutaneous hyperalgesia following local injuries to the skin. This hyperalgesia tended to spread over a relatively wide area surrounding the lesion and to endure for a matter of one or more hours. In normal circumstances, damage to the skin is the natural stimulus to the development of hyperalgesia, but under experimental conditions Lewis (1936) found that (i) crushing, freezing or faradizing tiny areas of skin; (ii) faradizing cutaneous nerve trunks, either through the skin or directly through subcutaneous electrodes, were equally effective.

The resulting hyperalgesia is a smarting soreness of the skin, spontaneous and on friction, and lends a peculiarly diffuse and long-lasting pain on pin-prick, and when a needle is mounted on a flexible hair pin-pricks are felt "more often" over a hyperalgesic than over a normal area. The topography of the hyperalgesic area has certain characteristics. To a tiny skin crush there ensues an oval area of hyperalgesia, to faradization of a nerve the hyperalgesia may fill the entire cutaneous distribution of the nerve. Hyperalgesia develops progressively after a delay of seconds or minutes, according to the intensity of the stimulus, and waxes and then wanes over a period ranging from one to several hours before it finally disappears. Not all subjects appear to yield the reaction, at least upon the occasions on which they were tested to this end—though Lewis does not make this important qualification.

In a series of further observations Lewis found that if an area of skin is anæsthetized before crushing, hyperalgesia does not develop until the anæsthesia passes off, when it appears in the usual way. Once it has ensued upon a skin crush, anæsthetizing the lesion does not abolish it. When the stimulus is faradization of a nerve trunk, blocking the nerve prior to, and proximal to the point of, stimulation delays the appearance of hyperalgesia until the block has passed off, when hyperalgesia develops as usual. But if before we stimulate the nerve we block it distally no hyperalgesia appears when the block passes off.

From the skin-crushing experiments, Lewis concludes that the production of hyperalgesia must be due to the

activity of cutaneous nerve fibres within the skin, the intensity, spread and rapidity of its development being incompatible with the simple notion of release and spread throughout the skin of a "pain-producing" (P-P) substance. Further, the delay in appearance of the reaction until the previously imposed anæsthesia of the damaged piece of skin has passed off, also indicates a nervous mechanism: while, finally, the fact that, once established, hyperalgesia is not abolished by anæsthetizing the lesion, indicates that a maintained flow of nerve impulses from the immediate region is not essential. From the faradization experiments he deduces that an ascent of impulses from the stimulated nerve to the central nervous system cannot be in question, since when the nerve is blocked above the stimulated spot —and no impulses can travel centripetally—impulses can still travel antidromically to the nerve-endings in the skin, where they suffice, as soon as the block passes off, to elicit hyperalgesia. The prior blocking of the nerve below the spot faradized does not prevent the central passage of impulses, but does prevent their passage distally to the nerve-endings, and in these circumstances no reaction ensues. Therefore, hyperalgesia must be due to the setting up of an altered state in the skin co-extensive with the cutaneous territory of the nerve stimulated.

The train of processes he supposes to be set up by damage to the skin is as follows :—

Damage to skin, local liberation of P-P substance.

↓

Stimulation of nerve endings in skin by this substance at the site of the lesion.

↓

Spread of nervous impulses throughout all or part of a cutaneous nerve distribution.

↓

Local liberation of more P-P substance at all endings of these skin nerves within this distribution.

↓

Lowering of threshold of all pain receptors in this area of skin.

↓

Passage of impulses centripetally along pain fibres to central nervous system.

↓

Hyperalgesia in affected area of skin.

It is the sole and essential function of the special system of cutaneous nerves concerned to cause the liberation in the skin of pain-producing substance, and the presence of this in the skin accounts for the persistence of the hyperalgesia, even when the damaged spot is anæsthetized and no nerve impulses are proceeding from it.

Lewis believes that the nerves in question cannot be the fibres and endings subserving pain because stimulation of a pain receptor yields a brief and accurately localized sensation of pain ; a response he regards as impossible in the case of such a cutaneous nerve plexus as he envisages. The wide spread of the hyperalgesia he attributes to the richness of the arborization of the parent nocifensor fibres when they enter the skin. He also speaks of the parent fibre as ultimately joining the posterior root fibres and entering the spinal cord.

Woollard's histological observations provide no evidence of the presence in the skin of any other system of branching nerve fibres with free endings than those demonstrably subserving pain, yet it is just such a system that Lewis postulates as present in addition to the pain-subserving fibres and endings, and just such a system that is found, in fact, capable of yielding a minutely and accurately localized sensation of pain. We see, therefore, that a nerve plexus can yield localized sensations, and that the only plexus of the kind known to exist subserves pain. There is no other. Another difficulty—if this were not conclusive enough—presents itself in the acceptance of Lewis's hypothesis. Let us try to construct a diagram of the nocifensor system, for if this has an anatomical existence it should be possible to represent it diagrammatically. At its distal extremity the nocifensor fibre ramifies to form an arborization of free nerve-endings in the skin, while proximally it runs up in the sensory nerve trunk to reach the posterior root and spinal cord. Its further fate and function therein *we are not told, but all that the hypothesis requires is a* cutaneous nerve plexus co-terminous with that of the cutaneous nerve within the territory of which it is found. No discoverable function can be conceived for a central prolongation of the nocifensor system into the central nervous system, for of itself the system subserves no sensory

function, and its activities are locally engendered and locally executed in the skin. The endings of the nocifensor plexus appear to be both receptor and effector, for when damaged an ending sets up impulses which travel throughout the plexus to all other endings, which then act upon skin cells; undamaged, the endings become effector themselves. In short, there are insuperable objections to Lewis's interpretation of his observations.

Nevertheless, some generalization of the facts of cutaneous hyperalgesia is called for, and, it is submitted, this may be found within the scope of what we already know about the structure and functions of the sensory nervous system. In respect of crushes of the skin, two results may follow: the stimulation of nerve-endings and fibres subserving pain, and the liberation from the damaged cells of the skin of "pain-producing" substance. Taking the first, and most certain, of these factors, the evidence points to the following conclusions. The unit of sensory reception for pain (as for other modes of sensibility) appears to comprise all the endings arising from a single parent fibre (presumably a posterior root fibre). This unit may be of relatively considerable dimensions on the surface and is also disposed in depth in the skin. Damage to any part of this unit affects the activities of the entire unit and may reasonably be assumed to set up a neural disturbance which arises from all parts of it. Further, as Adrian (1935) has shown, injury, particularly in sensory nerve fibres, sets up a rhythmic discharge in the nerve fibres. The discharge consists of a sequence of impulses of high frequency, sometimes of a recurrent discharge of from 2 to 20 impulses. How widely within the receptor unit this discharge may spread we do not know, but we may not assume that it occurs only within the limits of the actual crush.

That preliminary anæsthetization of the skin to be crushed delays the onset of hyperalgesia is inevitable; since inactivated fibres cannot be excited or impulses generated in them, and that subsequent anæsthetization of the crush does not abolish an already established hyperalgesia could be explained on the grounds given in the immediately preceding paragraph. The additional part played by

released "pain-producing" substance in reinforcing the "injury discharge" may be mentioned but cannot be assessed, but if it is operative and involves a larger territory than that anæsthetized, it would tend to add its influences to those of direct nerve injury. In this connection, we may recall Trotter's emphasis upon the "naked" and non-insulated character of the nerve-endings subserving pain sensibility, which would render them peculiarly responsive to chemical stimulants within the skin.

In the case of the hyperalgesia ensuing upon nerve trunk faradization, the factors operative are somewhat different. Here there is no local damage to cutaneous nerve-endings, but these endings receive a succession of impulses from above that may conceivably lead to the liberation at their endings of "pain-producing" substance. Whether this substance excites the endings without injuring them, or whether it constitutes a trauma, we do not know, but it is an agent of a kind that we should expect to set up prolonged activity in pain nerve fibres.

That blocking of the stimulated trunk above the spot stimulated should delay the onset of hyperalgesia is inevitable, since hyperalgesia requires for its appreciation an open pathway from skin to cerebral sensory centres. On the other hand, blocking of the nerve trunk below the spot faradized prevents the downward passage of nerve impulses to the skin endings and the resulting liberation of "pain-producing" substance.

In short, there appears to be nothing in these observations that requires us to postulate the existence of a special set of cutaneous nerves. Woollard's observations provide convincing evidence that the system of nerve fibres in question is that subserving cutaneous pain.

Other sensory modalities also arise for consideration in connection with pain: namely, tickling and itching. As Blake Pritchard (1932) has pointed out, the word "tickle" embraces two sensations differing in quality and in mode of elicitation. There is the superficial tickle that ensues when a hair or cotton fibre rubs along the thin skin of the lip or entry of the nostrils, and the deep tickle that follows firm pressure with the fingers down the sides of the chest or

in the axillæ. Superficial tickle requires a rapid sequence of discrete stimuli to tactile receptors, and in many regions of the body a wisp of cotton-wool drawn very lightly over the skin will elicit it. Pritchard has found that this sensation is abolished in cases of spinal cord lesion, *e.g.*, syringomelia, where cutaneous pain is abolished and light touch intact. On the other hand, when there is an intensification of cutaneous pain, *e.g.*, over the distal parts of the limbs in some cases of polyneuritis, he found superficial tickle intensified.

This suggests that tickle is a compound of touch and pain, or, as Pritchard believes, a minimal expression of pure pain, produced by the summation of a series of subliminal stimuli. The presence of an accessory fibre in each hair follicle, where it probably subserves pain, may have significance in this connection. Itching is probably also a variant of pain sensibility.

There are other problems of persisting pain following lesions of peripheral nerves that as yet have not found elucidation. Perhaps the phenomena of causalgia is the most striking of these. They may find their solution in the light of what we know of injury discharges in sensory nerves, and of the differential response to injury of the fibres subserving the various modes of sensibility.

In the category of spinal reflex reactions, Sherrington has spoken of what he calls " prepotent " reflexes : reactions that obtain control of the reflex paths and effector organs when these are played upon by multiple peripheral stimuli of different orders. Such a reaction is the nociceptive flexion reflex. In pain we may have on the sensory side a " prepotent " mode of sensibility, one that from its biological function has come to assume the dominating influence it has upon the sensorium. Just as its threshold is that appropriate to its function, so the sensory quality of pain is also appropriate to its end. Thus, we do not need to think of pain—as we experience it—as characterized by being a response disproportionate to the stimulus that excites it. Both threshold and response are, in fact, adapted to the rôle pain plays in the life of the organism. In short, pain is not the striking exception we often regard it as being to the rules that characterize other modes of sensory function.

In Head's hypothesis the localization of all modes of cutaneous stimuli is especially associated with tactile sensibility. As a component of his epicritic system it was a function of touch to correct the erroneous localization of painful and protopathic thermal sensations and to impart correct localization to them. How this was achieved was not described, but even for those who no longer subscribe to Head's hypothesis, the notion of touch as a peculiarly localizing mode of sensibility has lingered.

Thus, Blake Pritchard (1931) regards light touch (or light pressure, as he calls it) as being primarily and essentially a localizing function, which together with proprioceptive postural sensibility mediates spatial perception and discrimination. He bases this conclusion both on theoretical considerations and upon an experiment in which he used radiant heat as a stimulus. He did this to avoid that deformation of the skin which under normal conditions necessarily evokes tactile sensations. He used a heated platinum loop and believed that he was stimulating "heat spots" only, and whereas, using von Frey's hairs as a tactile stimulus he obtained an average error of 0·5 cm., with the heated loop there was an average error of over 1 cm. Lewis repeated this experiment, using a beam of light focussed upon the skin so as to cover an area of 4 to 5 mm. in diameter and there developing a temperature of 38° or 39° C. Pritchard made no skin temperature estimations, so that whether he was stimulating heat spots alone or also pain spots cannot be stated. Lewis obtained an average error of 1 cm. or less. Using a needle prick, Lewis found an error of less than 1 cm. Woollard's observations with needle prick are comparable with Lewis's. He found that two successive stimuli can be recognized as having been applied at different sites at a distance of 1 cm. on the forearm, 0·5 cm. on the palm and 1 mm. on the finger tips. It is true that in the last-mentioned experiments tactile sensibility was present, but they appear to indicate that its presence had no influence in increasing the accuracy of localization of painful stimuli.

Tactile sensibility is essentially a form of pressure sense, since deformation of the skin is the adequate stimulus to its receptors. Even the bending of a hair when the skin itself is not touched, involves deformation of the tissue immediately surrounding the hair bulb. Yet it has sensory qualities that distinguish it from deep pressure. Trotter has described the "pat" that constitutes a sensation of touch, and has said that introspectively it can always be differentiated from the sensation aroused by continued pressure. Electrical analysis confirms this distinction, as Adrian and his co-workers have shown, and it may be concluded that the two sensory modes possess end-organs and conducting fibres of specific function in each case. Stimulation of tactile receptors even when repeated at high frequency always yield discontinuous sensations, while increasing pressure yields a continuous sensation.

Yet the stimulation of a touch spot by a von Frey hair, however useful in the scientific investigation of sensibility, is the most artificial of stimuli when compared with the normal stimulation of the body surface during the life of the organism. In these circumstances receptors of both cutaneous and subcutaneous situation must be excited simultaneously and in sequence, and from the extent of the surface stimulated and the moving passage of stimuli across that surface, constellations of sensory impulses must arise and, reaching the integrating centres together with impulses generated in proprioceptors, provide the material out of which the perception of spatial relationships is elaborated. It must also be remembered that while during sensory investigations under the conditions of experiment the body surface is still and passive, during normal activity it is a moving receptive surface that, as it were, goes out to meet cutaneous stimuli and thus receives the most complex combinations and permutations of sensory stimuli. The rôle of tactile, pressure and proprioceptive modes of sensibility is therefore far more complex than those of painful and thermal modes.

IX.—Summary

In conclusion, lengthy as this review has been, it has not been possible within its scope to deal adequately with

every aspect of the problem, or even to mention the contributions of all the numerous workers who have added to our knowledge. Nevertheless, it is hoped that the salient features of the subject have been presented.

From the many and diverse studies considered, certain conclusions seem to be emerging. The doctrine of specific nerve energy receives support from clinical, physiological and anatomical sources, but it is not the individual impulse that shows specific qualities, but rather the entire sensory pathway, for each mode of sensibility, along which pass the streams of nerve impulses. It is specific in a physiological as well as in an anatomical sense: specific in the morphology, selective excitability and other qualities of the end-organs: in the grouping together from peripheral origin to central destination of the fibres that carry the impulses for each sensory modality: in the fibre types involved—and this in turn involves some specificity in the impulse potentials and in the conduction rates and excitability of the fibres: in the central excitatory states that modify each category of sensory impulse: and finally in the central destination of the impulses.

The long-established view that there are four primary modes of cutaneous sensibility, touch, pain, cold and warmth, also receives consistent support. Head's view that local sign in sensation and two-point discrimination are qualities inherent in the tactile impulse and are imposed by it on other modes of sensibility finds no support, and is incompatible with the results obtained in every field of research on sensory function.

Further, yet another conception is becoming clearer, namely, that of the physiological unit of sensory reception. Sherrington has shown that the physiological motor unit is the motor nerve cell and all the muscle fibres it supplies, some 150 or more. Reflex movement gradation is achieved by the fractionation of muscles into these groups. It seems that the unit of sensory function is similarly constituted: consisting of a posterior root fibre and all the end-organs (of a given mode of sensibility) that it innervates. Such a unit may reach macroscopic proportions, being disposed in the skin in area and in depth. Activation of a single

" spot " within this unit influences every other spot within it. The unit's complexity is reflected in the fact that each group of end-organs (touch, pain, cold or warmth spots) receives its principal innervation from no less than two nerve fibres, and that each individual end-organ receives also an " accessory " innervation which appears to endow it with pain sensibility when supramaximally stimulated. Before this conception can be regarded as fully elucidated and confirmed much has yet to be learned, but it is one in harmony with what we know of the management of movement by the central nervous system. The view that end-organs have a selective excitability is reasonably established, and the accessory nerve supply of end-organs clears up some of the difficulty that this conclusion has previously presented.

Much of the obscurity surrounding the anatomy and physiology of the mechanism subserving pain has been removed by the work of Woollard and his pupils; work which constitutes one of the most striking advances in our knowledge of sensory function within recent years. When its biological implications are fully taken into account, and irrelevant standards of assessment abandoned, pain sensibility appears not to differ essentially from other modes of sensibility.

Problems of localization and discrimination of sensory stimuli promise to receive a large measure of solution in the light of what we are learning of the nature of the physiological sensory unit, in which connection Tower's observations are of great significance.

On the negative side, it is clear that Head's theory of the morphological constitution of the afferent nervous system is invalid, and that Jackson's doctrine of release of function has proved singularly disappointing as a generalization of the observed facts of sensory loss from lesions of the nervous system. Possibly, it simply awaits a more penetrating application to these facts than it has yet received. Head's general theory is fatally handicapped by the attempted inclusion in it of a fallacious notion of the structure of the peripheral mechanisms of cutaneous sensibility. It attributes to simple conductors functions they cannot possibly subserve, and succumbs to the danger that always besets abstract

thinking; that of confusing thoughts with things, of hypostatizing abstractions. Those familiar with Faber's "Nosography in Modern Internal Medicine" will recall how the progress of medical thought was held up in the early years of the last century by the prevalence of abstract thinking and the false analogies it engendered. Further, Head's theory embodies views on the evolution of structure and function in the nervous system that find neither internal nor external corroboration, and are indeed incompatible with all we know of this evolution. Nevertheless, when all that is speculative and abstract is removed from Head's contributions to this subject, there remains a most impressive body of observation that must have permanent value and will serve as the material for a more realist interpretation.

Running as a recurrent theme through many of the writings on cutaneous sensibility we find a tendency, uniformly unfortunate in its results, to postulate anatomical structures without taking the steps necessary to establish whether or not they exist. Head's protopathic and epicritic fibres, Lewis's nocifensor nerves, and the hypothetical dual system of pain fibres for the conducting of the different sensory qualities of pain, all come to grief when they make contact with the hard facts of anatomy. Perhaps it is not the least of Woollard's services to science to have redressed the balance between anatomy and physiology in the study of sensory function.

With the increasing range and complexity of experimental methods, workers in the different fields inevitably show signs of isolation from each other's thought and of a lack of sound orientation in the general field of sensory function. The mass of literature that the past few years has provided has tended, also, to a neglect of the fundamentally important work on sensation of the closing years of the last century. The maximal exploitation of original observation in any single department of the general field can be attained only by those who are familiar with the results of research, old as well as new, in other departments. It is in connection with Trotter's contributions that this reflection seems most pertinent. To anyone who is actively thinking on the problems of cutaneous sensibility they are full of stimulating

thought and of sane realism. Thus, his surmise as to the basis of sensory hypoæsthesia, and his findings on the selective excitability of nerve fibres foreshadow the work of Woollard and the observations of the electro-physiologists. It seems likely, also, that his views on the insulation of the nervous system and on the peculiar structure of the pain nerve-endings may throw light on the abnormal patterns of innervation and the abnormal subjective sensory symptoms (*e.g.*, causalgia) that may ensue upon peripheral nerve lesions.

We have become too prone to regard the nervous system as a kind of ideal structure immune from the pathological reactions to damage that all other somatic tissues show, and thus as giving us a licence to speculative and abstract thinking about it that we would be wary of in respect of any other tissue.

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The Giant Cells of Betz, the Motor Cortex and the Pyramidal Tract

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SYNOPSIS

Chapter II

The Giant Cells of Betz, the Motor Cortex and the Pyramidal Tract

I.—Introduction

"*There is, perhaps, no subject in physiology of greater importance and general interest than the functions of the brain, and there are few which present to experimental investigation conditions of greater intricacy and complexity. No one who has attentively studied the results of the labours of the numerous investigators in this field can help being struck by the want of harmony, and even positive contradictions, among the conclusions which apparently the same experiments and the same facts have led to in different hands. And when seemingly well-established facts of experimentation on the brains of lower animals are compared with those of clinical observation and morbid anatomy in man, the discord between them is frequently so great as to lead many to the opinion that physiological investigation is little calculated to throw true light on the functions of the human brain. These discrepancies appear less unaccountable when the methods of experimentation and the subjects of experiment are taken into consideration.*"—Ferrier, Introduction to "The Functions of the Brain," Second Edition, 1886.

When Holmes and Page May (1909) undertook their investigation of the exact origin of the pyramidal tract, they recorded that "little or no precise information can be obtained on the origin of the pyramidal tract in even the later editions of the most authoritative textbooks on the anatomy of the nervous system."

By making use of the reactionary chromatolysis (retrograde degeneration, *reaction à distance*) and the subsequent changes which occur in nerve cells after division of their axones, they sought to determine the cortical cells which reacted thus after section of the corticospinal tract in the upper cervical region of the spinal cord, and might be considered therefore as the cells of origin of this tract. They performed hemi-section of the cord at the level of the first cervical segment in the cat, dog, lemur, macaque and chimpanzee, and these animals were sacrificed at periods ranging from five to 157 days subsequently, the cerebral cortex being then stained by the Nissl method and examined for cell changes. In addition, two human cases of severe traumatic lesion of the lower cervical cord were similarly

histologically studied. In these circumstances they found the reactionary cell changes confined solely to the giant cells of Betz in the paracentral lobule and in the upper part of the ascending frontal (precentral) convolution, and they concluded that these cells are the sole source of the pyramidal fibres. To this conclusion, they added some inferences that did not arise directly from their studies, namely, that the Betz-cell-bearing area of the cortex corresponds to the excitable motor cortex, and that both are co-extensive with Brodmann's area 4 of the frontal cortex.

If the method of reactionary chromatolysis be a valid one for this purpose, that is, if we may assume that *all* the cells giving rise to pyramidal fibres undergo this reactionary change when the corticospinal tract is divided, then it seems that we must accept the view that the Betz cells alone give rise to this tract. In fact, this view has been very widely accepted up to the present time.

Levin and Bradford (1938) have repeated these experiments in the macaque with almost identical results. They find retrograde degeneration in 81 per cent. of the Betz cells of area 4, and also in some of the "ordinary large pyramidal cells" of this area. Adjacent to degenerated cells were to be seen cells of fairly normal appearance. The authors point out that the smaller Betz cells are not always readily distinguishable from the large pyramidal cells, and express the view that "Betz cell" might be used as a term to include all cortical cells of whatever kind that send axones to the spinal cord. They believe that about 20 per cent. of pyramidal fibres arise from Brodmann's postcentral areas, 3, 1, 2, 5, and estimate the total number of cells of origin of the pyramidal tract in *macacus* as about 31,000, of which some 6,000 are postcentrally situated. This last group presumably corresponds to the giant cells of the fifth layer of the postcentral convolution in man, forming Economo and Koskinas's (1925) *area gigantopyramidalis postcentralis.*

This contribution provides an inkling of some of the difficulties that beset the attempt to attribute to the Betz cells the sole origin of the pyramidal tract; namely, the uncertainties inherent in the identification of the cells so

named. If our application of the title "giant cell" lacks precision or a generally accepted standard, then for us to assert that these cells alone give rise to the pyramidal tract is not to solve the problem of the origin of this tract, but to leave it still an open question. Indeed, our conception of the Betz cell is the crux, not only of this problem, but of several others of equal importance.

A study of the relevant literature shows, in fact, that the attribution to the Betz cells of the sole origin of the pyramidal tract is full of difficulties and unsolved questions. Some of these have long been apparent, but others have only recently come to light. Of the latter there is the striking discrepancy between the estimated totals of Betz cells in a single hemisphere (Campbell, 1905; Levin and Bradford, 1938; Lassek, 1940), and the total number of pyramidal fibres (Lassek, 1939, 1940, 1941 (*a*) and (*b*), 1942). The ratio between cells and fibres is as 1 : 40.

Difficulties of a physiological order have long been obvious, though of late years quite ignored. Thus, Horsley (1909), in his Linacre lecture, pointed out (in a passage cited on page 109 of this review) that in that part of the precentral convolution wherein are represented the movements of the head, of facial expression, of deglutition and of articulate speech, there is a virtual absence of Betz cells. Even earlier, Campbell (1905), the pioneer of cortical cytoarchitectonics, had drawn attention to the absence of "true giant cells" in this region, though he had noted the presence of "scattered nests of large pyramidal cells, which differ from those common to the whole precentral cortex in being more attenuated and in having longer processes and larger and more distinct chromophilic elements."

Even in the region wherein hand and digit movements are represented, the Betz cells are relatively scanty (as Figs. 9 and 14 reveal), though this region of representation is an extensive one. In all these circumstances it becomes difficult to credit the Betz cells with the exclusive origin of the corticospinal and corticobulbar fibres.

This mention of corticobulbar fibres, made by Horsley, draws attention to the fact that experimental section of the cervical cord can give rise to reactionary chromatolysis only

in that part of the precentral convolution in which movements of the limbs and trunk are represented. Yet the motor cortex must be taken to include the representation of the other movements enumerated by Horsley, a representation which is of the same physiological order as that of the movement of the limbs and trunk. The projection fibres from this representation run to motor nerve nuclei in midbrain, pons and medulla, and therefore it is essentially the relation of the Betz cell to what the clinical neurologist speaks of as the upper motor neurone that is in question.

Horsley's pertinent comment, to which attention was drawn in *Brain* by the present writer in 1935, attracted no attention, and this also has so far been the fate of the more fully reasoned objections on the same lines formulated by Economo and Koskinas in their important study of the cytoarchitectonics of the human cerebral cortex (1925). These authors draw attention to the fact, amply demonstrated by them, that the Betz cells are largest and most numerous where the extremely limited repertoire of simple movements of the muscles of the pelvis, perineum and lower limb are represented, but fewest and smallest where the fine but highly co-ordinated movements of the face and mouth, including those of articulate speech, are represented on the precentral convolution. The region representing hand and finger movements occupies the mean between these extremes, and they regard these facts as making it appear highly improbable that the Betz cells are the sole cells of origin of the corticospinal (and corticobulbar) fibres.

It becomes clear, then, that we need the precisest possible notion as to what constitutes a Betz cell before we can usefully consider its relation to the upper motor neurone, or say what rôle this cell plays in the formation and functions of the motor cortex. We must know whether the Betz cell is a specific morphological entity with functions peculiar to it, or whether it is simply the largest member of the large family of pyramidal cells. Involved in all these questions is the further one, at present a somewhat controversial question, as to what we refer to when we speak of the motor cortex. In the ensuing pages it is proposed to discuss these questions.

II.—The Giant Cells of Betz and other Pyramidal Cells of Areas FA and FB

(1) *Size and Appearances*

"*Die Physiologie hat auf allen Gebieten ihr sicherstes Fundament in der Anatomie. Wer physiologische Lokalisationsarbeit leisten will, wird daher seinen Forschungen die Ergebnisse der histologischen Lokalisation zugrunde legen müssen. Und mit mehr Recht als je darf heute an das vom Altmeister der Hirnforschung, Bernard Gudden, schon vor drei Jahrzehnten gegenüber einem einseitigen und gefährlichen Extirpations-spezialistentum gesprochene Wort erinnert werden; 'vor einer zweifellos bewiesenen anatomischen Tatsache verliert jedes physiologische Resultat, welches mit derselben in Widerspruch steht, seine Bedeutung. . . . Zuerst also Anatomie und dann Physiologie, wenn aber zuerst Physiologie, dann nicht ohne Anatomie.*"—Brodmann, "Vergleichende Lokalisationslehre der Grosshirnrinde," 1909.

Gudden's aphorism is very pertinent to our present review of the available facts of anatomy concerning the Betz cell in view of the edifice of hypothesis that has been built round the assumption that this cell alone gives rise to the pyramidal and corticobulbar fibres, and that it alone is the significant cell of the motor cortex.

In this chapter there are two anatomical questions to be considered, namely, that of cell types in the relevant cortical region, and that of their grouping and distribution therein. The last study is that now known as cyto-architectonics. Our sources include the studies of Campbell (1905), Brodmann (1909), Economo and Koskinas (1925) and Conel (1939, 1942). Reference must also be made to the work of C. and O. Vogt (1919) because, though this conflicts with that of all the other authorities named, it has been made the basis of recent experimental cortical physiology on the motor and so-called " premotor " cortex.

Not only have the various types of nerve cell in the cortex been described and classified, but these observers have also described the lamination of the cortex and its local variations. Brodmann divided the cerebral cortex into regions, and each of these into areas. The *region* with which we are concerned is known as the *regio præcentralis*, and it has been divided, on the basis of cellular and laminar peculiarities, into two areas. For these, each authority has coined his own nomenclature, and as it is necessary to use them all on occasion, they are given here. They are :—

1. The area immediately anterior to the fissure of Rolando :

Campbell's Area precentralis.
Brodmann's Area 4.
Economo and Koskinas's Area FA (including FAγ).
C. and O. Vogt's Area 4 (subdivided into *a*, *b* and c).

2. The area lying anterior to the preceding:
Campbell's Area precentralis intermedia.
Brodmann's Area 6.
Economo and Koskinas's Area FB.
C. and O. Vogt's Area 6 (subdivided into 5 subareas).

Together these two areas make up the agranular frontal cortex, so called because within it the two granular layers, II and IV of the cortex, are virtually absent. From the layers II to V inclusive the nerve cells are all of pyramidal type, and the cortex here is said to have undergone "pyramidization." Fig. 5 gives these two areas as delimited by Campbell, by Brodmann and by Economo and Koskinas. Foerster has also drawn up a map of cortical areas for man, but this is not based on direct histological study and is simply a copy of the cortical areal map of *cercopithecus*, drawn up by C. and O. Vogt, adapted to a diagram of the human cerebral cortex.

Before proceeding to a detailed description of the cell types and cell arrangements in areas 4 and 6, we may make the general statement that in these areas we find very numerous pyramidal cells covering a wide dimensional range from the smallest pyramidal cells at one extreme to the so-called giant cells of Betz at the other. These have been classified into a number of types, which tend to overlap dimensionally. Thus the smallest Betz cells are no larger than the largest of the "large ordinary pyramidal cells." This last fact suggests that size alone can hardly be a wholly satisfactory criterion of identity for the Betz cell, and when we come to examine the dimensional standards given by the numerous histologists who have studied the Betz cells we find that they vary very widely, and give the impression that the identification of the cell commonly so named, and known alternatively as the giant cell, must be a far less simple matter than is commonly assumed.

These dimensional standards are as follows :—

Betz	40 to 120 μ long by 50 to 60 μ broad.
Bevan Lewis . .	30 to 96 μ long by 12 to 45 μ broad.
Hammarberg . .	80 μ long by 40 μ broad.
Brodmann . . .	106 μ long by 53 μ broad.
Economo and Koskinas	50 to 120 μ long by 25 to 60 μ broad.
Conel (one-month child)	34 to 82 μ long by 10 to 23 μ broad.

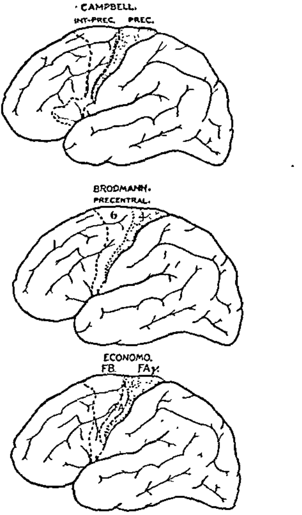


FIG. 5

The maps of Campbell, Brodmann and Economo and Koskinas on which the two component areas of the agranular frontal cortex (the regio præcentralis) are depicted.

Economo (1929) states that all pyramidal cells larger than 50 by 25 μ are to be called giant cells, and records that pyramidal cells of 65 by 30μ are to be found in layer IIIc of area FB, while in the one-month child Conel finds cells of 37 by 12 μ in layer V of the same area.

We may ask whether these varying criteria merely reflect the individual differences that are known to obtain, *or whether they express actual difficulties in identification*, or rather in differentiation from other large pyramidal cells. As will appear there can be no doubt that the latter factor plays a large part in these differences of standard. In the adult these figures give an extreme range of size for Betz cells from small cells of 30 to 12 μ to large cells of 120 by 60 μ. They reveal how loose is the appellation "giant cell" and what an exaggerated impression of the distinct individuality of this cell it conveys.

Size, then being plainly a very unsatisfactory criterion of identity, we turn to the microscopic appearance of the Betz cells as revealed by Nissl staining, or by silver-impregnation methods that reveal the silhouette of the cell body and processes. Even here we do not find any *absolute* criterion of difference between Betz cells and the largest pyramidal cells.

We find the most exhaustive comparative study of pyramidal cells of all types in the human cerebral cortex in the investigations of Economo and Koskinas, who give two standards of classification: one purely in the matter of the shape of the cell body, the other based upon Nissl and silver appearances.

(i) *According to Form.*—In this grouping the ratio $H \frac{B}{2}$ is adopted, where H is the height and B the breadth at the base.

(*a*) $H \frac{B}{2}$ is as 1 : 1 "plattgedrückte Pyramidenzellen."

(*b*) $H \frac{B}{2}$ is as 2 : 1 "flachdreieckige Pyramidenzellen."

(*c*) $H \frac{B}{2}$ is as 3 : 1 "mittelschlanke Pyramidenzellen."

(*d*) $H \frac{B}{2}$ is as 4 : 1 "schlanke Pyramidenzellen."

(*e*) $H \frac{B}{2}$ is as 5 : 1 "überschlanke Pyramidenzellen."

Of greater interest in our present connection is the second grouping :—

(ii) *According to Appearances in Stained Sections :*

(*a*) *Small pyramidal cells* $\frac{H}{B} = \frac{10 \text{ to } 15}{7 \text{ to } 10}\ \mu$. With a small oval nucleus and a single satellite cell.

(*b*) *Middle-sized pyramidal cells* $\frac{H}{B} = \frac{20 \text{ to } 30}{10 \text{ to } 20}\ \mu$. With a round nucleus near the base, nucleolus and one or two satellite cells.

(*c*) *Large pyramidal cells* $\frac{H}{B} = \frac{30 \text{ to } 50}{15 \text{ to } 20}\ \mu$. With a large clear nucleus, a dark nucleolus and two or three satellite cells.

(*d*) *Giant cells* ("*Riesenpyramiden*" *or* "*einfache Riesenpyramidenzellen*").—This category, not found elsewhere than in Economo and Koskinas's work, is scarcely larger than the preceding one, viz., $\frac{H}{B} = \frac{50 \text{ to } 60}{25}\ \mu$. These cells, however, are more massively built, and have a cytoplasm in which marked Nissl granules are seen. The nucleus is in the centre of the cell and the nucleolus is large. Of these simple giant cells the authors observe "Es ist oft schwer zu sagen, was man noch als Riesenzelle zu bezeichnen hat, weil sich alle Übergange von der einen zu der anderen Art vertreten finden," and again "Im Einzelfälle oft schwer is to unterscheiden, zu welcher Gruppe das einzelne Individuum gehört, da alle möglichen Übergansstufen zu finden sind."

It is noteworthy that these cells are to be found in *all* parts of area FA in layers IIIc and V.

(*e*) *Betz giant cells* ("*Betzsche Riesenpyramiden*" *or* "*Kolossalzellen*").—These include the largest nerve cells in the entire cerebral cortex, but the smaller members of the group are no larger than cells of the two preceding categories. They range in size from $\frac{H}{B} = \frac{60 \text{ to } 120}{40 \text{ to } 60}\ \mu$, though according to other writers, cells of even smaller dimensions are named Betz cells. These cells have a typically tall build, and in outline vary somewhat, being described as pyramidal, pyriform or like a burgundy bottle On the buried surface of the precentral convolution where they lie in the fissure of Rolando, they tend to be less well-formed, and distorted in outline. They lie almost exclusively in layer V, though

occasional specimens are to be seen "disloziert" in layers IV and IIIc. They are confined to area FAγ. Their dendrites are stout and knotted in appearance, so that by silver impregnation methods the cell and its processes resemble a tree with roots and branches. This appearance is beautifully illustrated in Fig. 6, taken from Conel's atlas of the cortex in the one-month child. The cell body contains numerous large Nissl granules (from 4 to 6 μ in diameter) and stains darkly, so that in stained sections the cells can be seen as darker spots to the naked eye. The nucleus is a clear bladder-like structure of some 25 μ diameter, and contains a dark nucleolus that may measure from 4 to 7 μ in diameter. From 5 to 6 satellite cells accompany each Betz cell. Lying in close proximity to these cells are very numerous simple giant cells and large pyramidal cells, and speaking of them Economo and Koskinas say: "Naturlich finden sich alle Übergange in Grösse and Form von diesen Riesenpyramiden einerseits zu den Betzschen Kolossalzellen, andererseits, wieder nach ruckwärts zu den gewöhnlichen grossen Pyramidenzellen." Betz cells are found in small nests of from 3 to 8, and these together form larger aggregations, as Betz (1874), Bevan Lewis (1878) and Campbell (1905) have all noted. Thus, even within area FAγ they do not form a continuous field.

From this classification it appears that Economo and Koskinas have felt it necessary to formulate two categories of giant cell, differing not qualitatively, but in degree of size, massiveness of form, size and abundance of Nissl granules, and in stoutness of processes. The larger group (Betz cells) are said to be restricted to area FAγ and to layer V, the simple giant cells are found over the whole of area FA, and in two cortical layers, IIIc and V. In the former layer they are also found at the hinder ends of the frontal convolutions where areas FA and FB meet.

Classification thus provides us with three categories of large pyramidal cell; Betz cell, simple giant cell and large pyramidal cell, but it seems clear that every possible transition form between the members of this conventional grouping is to be seen, not only in the adult cortex as reported by Economo and Koskinas, but also in the infant cortex as

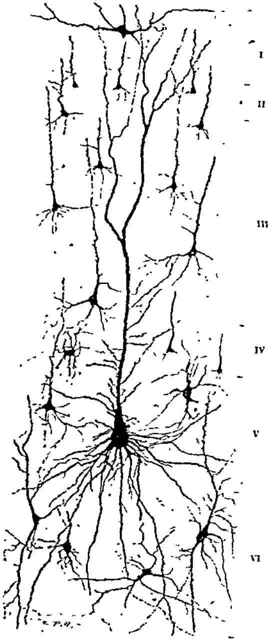


Fig. 6

A camera lucida drawing of the cortex of the paracentral lobule stained by the Golgi-Cox method. Fig. 18 of Conel's Vol. II, on the cortex of the one-month child (Harvard University Press).

recorded by Conel (1942). At one extreme we have the Betz cell with its numerous large Nissl granules, at the other the slenderer large pyramidal cell which only exceptionally contains distinct Nissl granules, but the series is continuous, and we can no longer accord the Betz cell the exclusive position we have hitherto given it as a specific entity with functions exclusive to itself. The Betz cell is no more than the largest and most massive member of the large group of pyramidal cells. This is, indeed, the conclusion to which Economo and Koskinas arrive, and they state that "dieseverschiedene Zellen also nicht anderes als durch ihre Grösse unterschiedene Individuen ein und derselben Zellart sind" (page 290).

For purposes of description, classification is necessary, but having once made our groups, we are too ready to assume that we have discovered essential qualitative distinctions that may have no reality in nature. It may be suggested that this has been the case with the giant cell of Betz, and the Russian histologist could have chosen no more striking word than "giant"—with its emotive background of nursery mythology—to impress us with a sense of the exclusiveness of the cell he so described, and to perpetuate that impression despite the accumulating weight of evidence that it has no real foundation in nature.

(2) *Distribution in Areas FA and FB*

If the microscopic study of stained pyramidal cells has failed to establish the specificity of the Betz cell, it remains to be seen whether the distribution of this cell within the cortex confers exclusive qualities upon it. If for the moment we exclude from consideration large pyramidal cells and simple giant cells that, as seen in Nissl stained sections, may present difficulties in classification, there remains a considerable group of what all would regard as Betz cells. These are the larger members of the group so named. In man, these are found only within that posterior part of area FA that Economo and Koskinas call FAγ or the *area giganto-pyramidalis precentralis.*

The limits of this area are fully depicted in Fig. 7, which is made up of Figs. 133*a* and 133*b* of Economo and Koskinas

superimposed. The figure also gives the limits of the whole area FA. It will be seen that at the level of the third frontal convolution the Betz cell distribution has sunk entirely into the depths of the fissure of Rolando. The lower limit of Betz cell distribution is reached at a distance of from 2 to 4 cm. above the fissure of Sylvius.

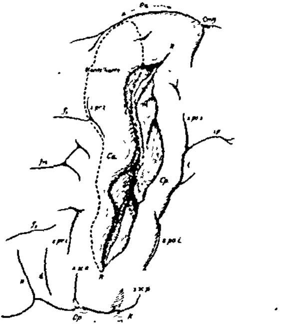


Fig. 7

Economo and Koskinas's Fig. 133a, with the limits of areas FA and FAγ superimposed from Fig. 133b (Economo and Koskinas, p. 522). The paracentral lobule is represented as though in the same plane as the convexity of the hemisphere, and the mesial fissure is represented by a dotted line and the word "Mantelkante." The fissure of Rolando is opened so as to show its floor. Area FA is demarcated by an interrupted line, and the anterior limit of area FAγ by a dotted line.

It might easily be concluded from the linear boundaries given to the Betz cell distribution that these boundaries were clear-cut and unequivocal. This is undoubtedly true of the posterior boundary which lies almost at the bottom of the fissure of Rolando, some 2 mm. from its floor and on the anterior wall of the fissure. The limits of these cells on the mesial aspect of the hemisphere in the paracentral lobule are also fairly clear, but the anterior border of the Betz-cell-

bearing area is quite another matter. As *we trace the* Betz cells forwards from the fissure of Rolando towards the anterior border of area FAγ, they diminish progressively in size and their differentiation from simple giant cells and from some large pyramidal cells becomes increasingly difficult. The simple giant cells are found over the whole of area FA in layers IIIc and V. The anterior border of Betz cell distribution is a sharp one only if we take the most *anterior cell we detect in a section and call that a sharp border, but if we take the field of Betz cells as a whole there* is no such border. In the one-month child Conel confirms the transitional passage from Betz-cell-bearing to Betz-cell-free areas. He says the decrease in cell size " is so gradual that there is no abrupt boundary between Betz cells and the extra large pyramidal cells in layer V, so that it is impossible to say where the giant pyramidal cells end and the extra large pyramidal cells begin. . . . The cells and their dendrites *gradually decrease in size towards the anterior wall of gyrus centralis anterior, but even here some of them are* as large as the largest cells in the posterior wall of the gyrus. On the basis of cell size it is difficult to say where area FAγ ends and FA begins " (p. 12).

Again, " there is no abrupt change from giant cells to extra large pyramidal cells, therefore it is impossible to say where the one type ends and the other begins " (p. 17). *In short, the anterior limits of the Betz-cell-bearing area do not admit of linear or precise definition.*

Economo and Koskinas's placing of the anterior fringe of Area FA forwards of that of FAγ is explained by the fact that they have delimited their cortical area, not in respect of a single cellular element, but in respect of the " Gesamtbild " of the area ; that is, of all the features of all the cortical layers. Comparison shows that their area *FA is slightly more extensive than Brodmann's area 4, an indication that cortical map-making is not an exact process* but a matter of broad distinctions and approximate estimates.

Within the generally accepted area of their distribution the arrangement of the Betz cells presents certain characteristic features. In a recent study, Lassek (1940) finds that in an estimated total of 34,000 in a single hemisphere, 75

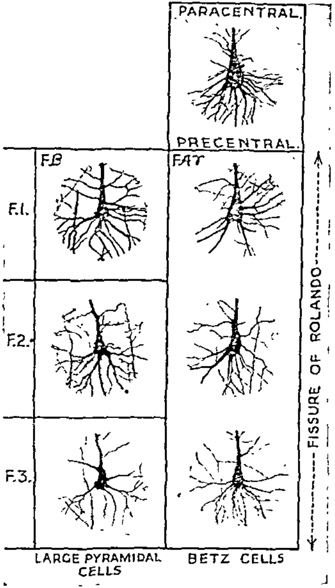
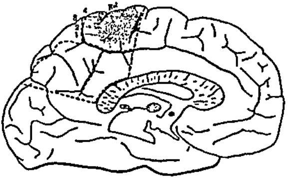
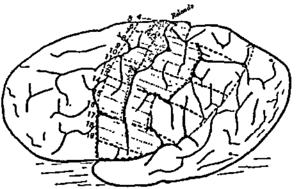


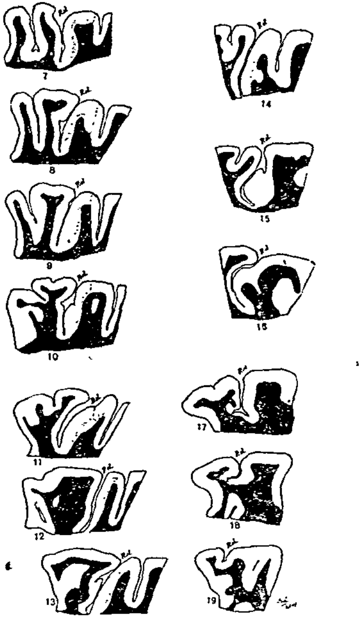
Fig. 8

Drawings of Betz cells and large pyramidal cells in layer V of area FA and area FB. The cells are all placed within a conventional scheme that represents the fissure of Rolando, the paracentral lobule and precentral gyrus. F1, F2 and F3 represent the three frontal gyri, and the cells are placed according to their actual position in the cortex. The diagram shows the diminishing size of the cells as we pass from the upper to the lower part of the cortical surface. These cell drawings are from Conel's (Vol. II) Figs. 18, 22, 26, 30, 34, 36 and 42. They reveal the large dimensions of the large pyramidal cells of the posterior part of area FB and their general resemblance in form and proportions to the giant cells of area FAγ.

per cent. are to be found in the medial third of the Betz-cell-bearing area, 17·9 per cent. in the middle third, and only 6·6 per cent. in the lower third (see Fig. 14). Also, of the total, not less than 82 per cent. are buried in the







Reproduced by arrangement with the Cambridge University Press from Campbell's "Histological Studies on the Localisation of Cerebral Function."

Fig. 9

Campbell's Plate IX. It illustrates the distribution of the giant cells of Betz, which in the cortical map are marked by dots, and by dots also in the sections of the cortex, which are numbered in correspondence with the map. It will be seen that the majority of Betz cells lie in the anterior wall of the fissure of Rolando. In the original plate the situation of cellular changes associated with tabes dorsalis in the postcentral gyrus was indicated by crosses. These have been deleted as not relevant, and for the sake of clarity.

anterior wall of the fissure of Rolando, only 18 per cent. lying on the free surface of the convolution. Other numerical estimates of these cells are Campbell's of 25,000 for man, and Levin and Bradford's of 31,000 for macacus, of which they find 6,000 in the postcentral convolution. From what has been said of the difficulties inherent in a precise identification of the Betz cell, these estimates must present a considerable margin of potential error. It has already been mentioned that the largest Betz cells are found in the paracentral lobule, the smallest at the anterior fringe of their distribution and in the lower end of the precentral convolution: that is, where they are largest they are most numerous, least numerous where they are smallest.

Reference has been made to the grouping of Betz cells, and in view of the suggested identification of the Betz-cell-bearing area with the "motor cortex" it is interesting to note that, while the latter is a continuous region with no constant silent areas within it, the Betz cell is not distributed in a continuous layer, but in a number of groups between which lie Betz-cell-barren areas. These groups have been described by Campbell as follows: (*a*) nests of enormous Betz cells in the posterior two-thirds of the paracentral lobule; (*b*) dense clusters of cells at the broad upper extremity of the precentral gyrus just lateral to the border of the hemisphere; (*c*) cell clusters on the free surface of the gyrus at the posterior end of the first frontal gyrus; (*d*) cell clusters at the level of the superior genu of the fissure of Rolando; (*e*) smaller cell clusters immediately below the genu. That is the lowest important and constant group, but, lower, two smaller and variable groups may be found. Between groups (*d*) and (*e*) is an area constantly barren of Betz cells at the level of the annectant gyrus of the fissure of Rolando. Campbell's Plate IX, here reproduced, shows the total distribution of Betz cells on the cortical surface and in sections of the precentral gyrus (Fig. 9).

When we come to consider the distribution of the *simple giant cells* and of the *large pyramidal cells*, we find that while the superior and posterior limits of this are the same as for the Betz cells, the anterior and lower limits extend over a larger area. Simple giant cells are found over the entire

area FA and in layer IIIc as well as in layer V. Economo and Koskinas say of them that "wir sprechen aber solche Zellen trotzdem als Riesenzellen an, wenn did durch ihre unmittelbare Lage zu den anderen kolossalen Betzschen Zellen und durch ihre übrigen Merkmäle sich als zu ihnen gehörig erweisen . . ." (p. 63). Their arrangement in layer IIIc is not quite the same as it is in layer V, for while in the latter they tend to diminish in size as we follow them forwards and down over the surface of the hemisphere, in layer IIIc they are largest at the meeting of areas FAγ and FA, and even trespass on to area FB in the pars triangularis of the third frontal convolution (*cf.* Fig. 11).

The large pyramidal cells extend even further forwards well into area FB, and in layer IIIc reach their largest dimensions in this area. Further, in layer V, the large pyramidals become more numerous at the lower part of area FAγ, and they seem to substitute for the Betz cells which disappear here from the cortex. Economo and Koskinas state that "dieses grossen und ganz grossen Pyramidenzellen sind speziell in der Gegend des Handzentrums und auch besonders in den ventralen Teilen der vorderen Zentralwindung in ausserordentlichen Anzahl und Grösse vertreten, also gerade da, wo die Betzschen Riesenzellen beinahe fehlen. Dies legt den Gedanken nahe, dass hier vielleicht eine ganz bestimmte Beziehung zwischen diesen Zellen verschiedener Grösse bestehen konnte." Between these large pyramidals and the Betz cells they add, "alle möglichen Übergange und Zwischenstufen" are to be found, and they deem it likely that while the Betz cells are functionally related to large and simple movements of trunk and lower limbs, the more numerous large pyramidals serve a like rôle in respect of the small, finely co-ordinated movements of head and upper limbs.

Prominent as are these large pyramidal cells in layer V of area FA, they are an even more striking feature of layer IIIc, of which in area FB they form the most characteristic feature. So well do they stain that in Nissl sections they can be seen by the naked eye in area FB as a dark line. They vary in size from 35 to 80 μ tall and 20 to 30 μ broad at the base, and they really come within Economo and Koskinas's

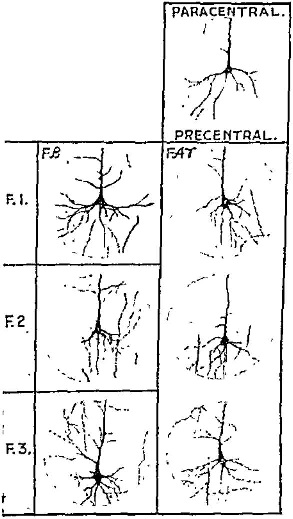
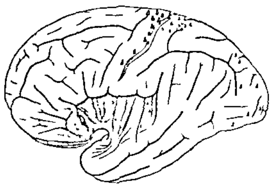


Fig. 10

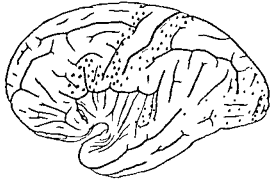
Drawings of large pyramidal cells in layer IIIc of area FAγ and area FB. They are arranged on the same topographical plan as in Fig. 3, and are taken from the same drawings in Conel's Vol. II. It will be seen that the large pyramidal cells are larger in area FB than in the paracentral lobule and area FAγ.

standard of size for simple giant cells. They are the largest pyramidal cells in the cortex after the Betz cells. Their apical dendrites may be followed towards the surface of the

cortex for as far as from 100 to 120 μ, and as Economo and Koskinas's figure shows (Figs. 11A and 11B below), they are largest at the hinder end of the first and second frontal convolutions. Definite Nissl granules are only exceptionally seen in them, but they have a large, clear centrally situated



A



B

FIG. 11

Economo and Koskinas's Figs. 79 and 74 respectively. A represents the the distribution of giant cells in layer V. B represents the distribution of the large pyramidal cells of greatest size in layer IIIc.

nucleus, a deeply staining nucleolus and two or three satellite cells. As many as eighteen of these large cells may be seen in 0·1 c.mm. of tissue, a greater number than we find of Betz cells in the same-sized unit.

It has been necessary to go into this detail concerning the various types of pyramidal cell in areas FA and FB to show that the facts in connection with them are far more

complex than we may gather from the brief accounts commonly given. Both areas FA and FB are rich in large pyramidal cells. In layer V the size of these diminishes as we trace them forwards, and as they become smaller they lose progressively the features we have learned to look for in the Betz cell, but the change is a progressive and not a sudden one. In layer IIIc (and to a lesser degree in IIIb) the simple giant cells spread more widely than in layer V *and cover the whole of area FA, but the large pyramidals* tend to increase in size as we pass from FA to FB, and reach their maximal dimensions just over the border of the latter area, then again decreasing in size as we pass forward in the direction of FC. FA and FB differ most obviously in the disappearance of Betz cells in the latter and in the great development of large pyramidal cells in layer III of FB. In brief, the resemblances between areas FA and FB are greater than their differences and the border between them is *characteristically lacking in sharpness,* at least as far as layer V is concerned. It is the "Gesamtbild" of each area that justifies it being regarded as distinct, and it is in virtue of the "Gesamtbild" of area FA that Economo and Koskinas postulated an anterior Betz-cell-free part of area FA, the Betz-cell-bearing part being known as *FAγ* or the area gigantopyramidalis precentralis.

So far, we have discussed the human cortex *only,* but since apes of the genera *cercopithecus* and *macaca* are largely used in the experimental physiology of this region, some reference to the cellular forms and cytoarchitectonics of these animals is necessary. Brodmann has provided areal maps and cell descriptions of these. In these animals there are areas 4 and 6 homologous with those found in man, *and together constituting an agranular frontal cortex.* Area 4, the Betz-cell-bearing area in these types is of wider extent than in man and covers the precentral convolution. It is not, however, sharply demarcated from the area (6) lying immediately anterior to it, and it is useful to cite Brodmann's account of this border. Thus, he says (1909, p. 135), "Ziemlich unbestimmte und schwankend ist die *orale Grenze der Area gigantopyramidalis auf der Kon*vexität, da Feld 4 and 6 fliessend ineinander übergehen

und da namentlich vereinzelte Betzsche Riesenzellen in 'solitärer' Anordnung bald mehr bald weiniger weit oralwärts zerstreut liegen, so dass die Festlegung der Übergangslinie rein subjektiv ist und nur aus zahlreichen Individualgehirnen gestimmt werden kann."

The map of cortical areas in *cercopithecus* that we owe to C. and O. Vogt presents a difficult problem of assessment, for it differs in essential characters from the cortical maps

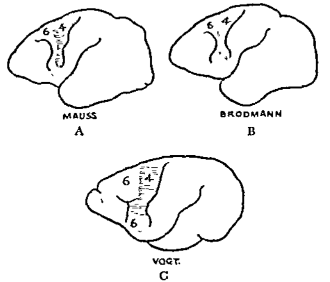


Fig. 12

A represents Mauss' myeloarchitectonic map of *cercopithecus*, B is Brodmann's cytoarchitectonic map of the same type, and C is the Vogts' map for the same type.

of all other observers, both of monkeys and of man. Whereas there is general agreement that cortical areas with few exceptions are not sharply separated, but merge into one another, and that each component cortical layer tends to have its own transition fringe, the Vogts maintain categorically that all cortical areas are typically separated by "haarscharf Trennungslinien," that each area, physiologically considered, is equally sharply differentiated in respect of its functions, and that the dividing lines tend to be regular. For them the cortex is built on a chessboard or mosaic plan, both anatomically and physiologically.

superior and posterior limits, but at the anterior limits varying in extent, smallest in the case of the Betz cells, slightly larger for the simple giant cells, but largest for the large ordinary pyramidal cells. These anterior limits are nowhere sharp for any of the three categories, Betz cells passing gradually into simple giant cells, and these into large pyramidals.

Within this general field of pyramidal cells of layer V, covering area FA and the adjacent posterior part of FB it is difficult to detect any inner dividing border separating qualitatively distinct components.

We have seen that the cortical areal map, such as that of Economo and Koskinas, is based expressly upon the "Gesamtbilder" of the areas it depicts. Within a given area, as these authors point out, each layer undergoes its own variations independently of those of the remaining layers. Thus one layer may extend unchanged into an adjacent area, while another undergoes considerable change within the limits of a single area. The areal map is therefore a composite affair. It strikes an average, as it were, between the competing claims of each of the six layers for representation. *It does not, therefore, strictly speaking, represent structure with anatomical precision.* When we come to equate a cortical physiological mechanism, *e.g.*, the motor cortex, with the cytoarchitectonics of the region in which we find it, we have to ask ourselves with what precisely are we to equate it—with the "area" or with the lamina?

In a given area, one or more of the cortical cell layers may have no part in the activities of the physiological mechanism we are considering. There are reasons for believing, for example, that the motor cortex and its projection the pyramidal tract are largely, if not wholly, based upon the fifth cortical lamina. This we have seen to possess a structural uniformity over an area wider than that of cortical area 4, namely, over the whole of area 4 and the adjacent posterior part of area 6 (that is, FA and part of FB). *Therefore, in attempting to correlate functon with structure, perhaps we should concern ourselves, not with area 4, but with layer V in areas 4 and 6.* With these considerations in mind, it seems that in future, we may have to direct our attention to a laminar

physiology of the cortex rather than—as we have hitherto done—to an areal.

Possibly we shall have to consider layer V as constituting one physiological mechanism and layer III as providing the anatomical substratum of another. Moreover, it is well to remember when thinking in terms of cytoarchitectonics that function is not simply a matter of nerve cells, or of nerve cell bodies, but of the infinitely complex anatomical and physiological relations set up between these cells by means of their processes. It is at the synapse that occur the grading and interaction of excitation and inhibition, and synaptic arrangements occupy a place of primary importance in cortical structure and function. Therefore, the correlation of function and structure involves more than a study of cortical cytoarchitectonics.

In conclusion, an interesting sidelight on the probable physiological unity of cortical layer V over areas 4 and 6 is to be found in the observation recorded by Howe and Bodian (1942) to the effect that the virus of poliomyelitis shows a specific affinity for the nerve cells in these two areas. A glance at their Plate XXII suggests that this affinity is confined to some only of the cortical layers, apparently from III to V.

III.—The Relation of the Betz Cells to the Motor Cortex

"*When the discovery of 'motor centres' first attracted attention, Dr Bevan Lewis, as long ago as 1878, showed that the precentral gyrus contained giant pyramidal cells in groups, and he mapped out this part of the cortex as being specialized for motion. Possibly because the groups of these giant cells did not correspond to the foci of representation as demonstrated by the method of excitation, and possibly also because (as he showed) there are areas of the motor cortex where no such cells exist, his observations did not attract the attention they deserved.*"

"*To include the whole efferent or motor area as determined by excitation we must take two of Campbell's regions, both his intermediate precentral and his precentral areas, though he wishes, apparently, the term 'motor' to be restricted to the latter. This suggested restriction of the term 'motor,' namely, because the giant pyramidal cells of Betz are to be found in only a certain (the major) portion of the precentral gyrus, cannot be justified, since it would exclude the motor centres for the face, larynx, pharynx, and eye muscles, as well as part of the representation of head movements.*"—Victor Horsley, Linacre Lecture, 1909.

These two passages from Horsley indicate how widely physiological opinion moved after the date of Campbell's

the most part in the intermediate precentral area of Campbell. Opposite the 'arm area' it lies not far behind the anterior border of the intermediate precentral area, but opposite the 'leg area' it lies very much further behind the anterior limit of intermediate precentral area, although in front of anterior limit of the pure precentral area of Campbell."

For the anthropoid apes, therefore, the motor cortex is the area thus experimentally delimited, and its anatomical substratum is seen to include the whole of Brodmann's area 4 and also the adjacent and posterior part of his area 6.

In man the situation is not different, and in the stimulation studies of Penfield and Boldrey (1937), the most recent of the kind, we find the motor cortex a well-defined area embracing precisely the regions named by Leyton and Sherrington.[1] These observers state that without any increase in stimulation strength, motor responses of uniform character are found in area 4 (FA) and the adjacent part of area 6 (FB), "*with no particular tendency to follow the cytoarchitectural pattern.*" Even Foerster, whose standardization of experimental conditions appears to have been very imperfect (1931), and whose conclusions differ from those cited in some respects, reports that "stimulation of points of area 6aα (the Vogts' nomenclature) produces the same isolated effects that are obtained from stimulation of area 4, and there is the same subdivision into foci for single segments of the limbs, but the threshold is much higher."

Whence, then, the present confusion? Until 1932 the conception of the motor cortex as something purely within the physiological category held the field. It is true, that by many—though not by all—the motor cortex was believed to be anatomically co-extensive with the Betz-cell-bearing area, yet it remained a term with physiological reference. In this year a new conception was formulated and later expressed thus by Fulton (1933-34): "The motor area is defined histologically as the region of the cortex containing in its fifth layer the large cells of Betz. It should be

[1] Penfield and Boldrey also record the presence of some excitable points in the postcentral convolution. Concerned only to determine the topography of the excitable motor cortex, they appear to accept without critical examination the hypothesis that restricts the motor cortex to area 4, and they assume that all motor responses evoked by them from area 6 are really due to activation of area 4. This assumption does not follow from any facts they record.

emphasized that the limits of the motor area are determined by its cellular structure and not by its electrical excitability." Here the physiological properties of the motor cortex are explicitly rejected as irrelevant and an anatomical hypothesis —that is yet to be proved—put in their place as the essential criterion of definition.

Confusion followed fast upon this new definition, and it soon became necessary to restore electrical excitability—though with qualifications—to the definition. Thus, Fulton (1938) says that "the excitability of area 4 in the higher primates and man differs from that of other motor regions of the cortex in the discreteness of its responses," and again (1936) "the functions of the anterior part of the excitable cortex obviously differ from those of the posterior." This anterior part is known as the "premotor" cortex, and its anatomical definition suffers the same confusion as that of the motor cortex. Thus, Bucy (1933) states that the premotor cortex is (*a*) the cortical region immediately anterior to the "classic motor area" and is also (*b*) co-extensive with area 6. Yet, clearly, it cannot be both, for the classic motor area can be no other than that of Leyton and Sherrington which we have seen to include part of area 6: that is, part of what we are now asked to call the premotor cortex. Finally, we find Fulton and Dusser de Barenne (1933) using the terms "excitable cortex" as synonymous with "motor cortex," and Fulton (1935) stating that "the term 'excitable area' is applicable to both the motor and premotor regions."

In short, the term "motor cortex" is now used in purely opportunist fashion, and it has ceased to be a term of precision.

A prime necessity in the grammar of science is an unequivocal terminology, each item of which refers to one thing or to one notion, and not to any other thing or notion. Without this, clarity of thought and the interchange of ideas are alike impossible. The motor cortex was originally so named in virtue of certain physiological properties it displays and for no other reason. Indeed, there could be no other valid reason, for in physiology the adjective "motor" has functional and not structural reference.

When we refer to a nerve cell as a "motor" nerve cell we refer to the functions of that cell, its morphology being for the moment indifferent. The same consideration applies to the use of the term "motor cortex" or "motor area." We here refer to function, and function cannot be "defined histologically," but only in terms of function. To specify

the anatomical substratum of the motor cortex calls for a statement additional to that defining function. Fulton's new definition confuses the anatomical and physiological categories, and declares irrelevant those very properties from the possession of which the motor cortex derived its name.

It is surely clear, therefore, that we must return to the physiological definition of things and notions physiological. Hence, in this review, by the term "motor cortex" we refer to the cortical region delimited physiologically by Leyton and Sherrington in anthropoids, and by Penfield and Boldrey in man. If we now compare the maps of the two former for orang and gorilla and of the latter for man, with Campbell's chart of the distribution of the Betz cells, a distribution regarded as co-extensive with area 4 by all observers prior to Economo and Koskinas, we see that the stimulation maps agree in showing a *uniformly* excitable region of cortex that embraces area 4 (FA) and part of area 6 (FB). In none of these types is the motor cortex co-extensive with the Betz-cell-bearing area 4 (Fig. 9).

We may now proceed to consider the objections that may be urged against this conception of the motor cortex. These are of two orders: one anatomical, the other physiological. They are as follows:—

(1) It has been said that the anterior border of the physiologically delimited motor area is too vague for purposes of definition, and is incapable of anatomical correlation. Forty years ago, this objection might have carried some weight, but it has long since been obsolete now that we have authoritative experimental evidence in anthropoids and man as to the place and quality of this anterior border. Leyton and Sherrington found that under the influence of "facilitation" the anterior border of their motor cortex can be slightly advanced. This variation is the measure of the vagueness alleged, and it is a variation inherent in the very nature of cortical function and is neither incomprehensible nor capricious. Further, so far from providing a contrast with anatomical aspects of the cortex, it accords remarkably with these. As we have seen, there are, in fact, no "hair-sharp" lines dividing the different cortical areas on cytoarchitectonic grounds, save for a few known

exceptions which do not include areas in the frontal lobe. Nothing emerges more clearly from the studies of Economo and Koskinas than the difficulties involved in any precise delimitation of cortical areas, and what Brodmann has to

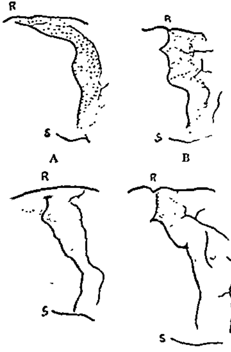


FIG. 13

These diagrams represent in the stippled areas the excitable motor cortex as physiologically delimited. A in the orang, B in the gorilla, C in man. D represents Campbell's chart of the distribution of Betz cells in man and is given for comparison with the extent of the motor cortex. (A and B from Leyton and Sherrington, 1917. C from Penfield and Boldrey. D from Campbell's Plate IX.) R is the fissure of Rolando, S the fissure of Sylvius.

say on the matter in the case of areas 4 and 6 of *cercopithecus* we have already seen. The areas depicted on a cortical map attempt to take into account all the six component layers of the cortex, and, as it were, to strike an average between them ; but an ideal cortical map would require a separate sheet for each layer, and, in short, as Economo and Koskinas remark, there is about the border of any cortical area something arbitrary and subjective, dependent upon

the particular cell form or lamina we chance to have under consideration. Thus, cytoarchitectonics provide us with nothing more precise than does physiological experiment, for the simple reason that the cerebral cortex is not built as

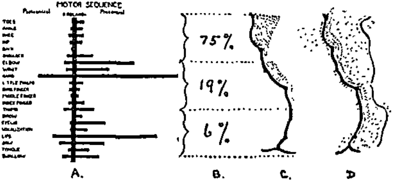


Fig. 14

A diagram showing the relation of the cortical representation of movements in the human cortex (Penfield and Boldrey) with the Betz cell distribution. A Penfield and Boldrey's motor sequence chart. The list from "toes" to "swallow" indicates the sequence of motor responses in the Rolandic cortex from the median fissure above to the Sylvian fissure below. The length of the individual horizontal lines to the right indicates the proportional number of points anterior to the fissure of Rolando yielding the movements named. Their length to the left indicates the number of responses evoked from the postcentral gyrus. B gives Lassek's figures for the relative distribution of Betz cells in the three-thirds of the Betz cell area. C gives Campbell's diagram of Betz cell distribution. D gives the extent of the motor cortex as delimited by stimulation by Penfield and Boldrey.

a chessboard. It seems safe to say that neither anatomy nor physiology provide us with any reality corresponding to cortical maps such as those of the Vogts and of Foerster. These constitute a highly artificial two-dimensional scheme of a three-dimensional anatomy, and they depict a simplicity in natural objects of which nature knows nothing.[1] There

[1] In a recent paper essential to any student approaching this subject, Lashley and Clark (*J. comp. Neurol.*, 1946, 85, 223) confirm these strictures. They observe that "in planning experimental work on the cortex it is desirable to have some guide to probable functional units in order that the work should not be undertaken wholly at random. For this purpose, however, the 'ideal' architectonic chart is nearly worthless, because individual variation is too great to make the chart significant for a single specimen, because the areal subdivisions are in large part anatomically misleading as to the presumptive functional divisions of the cortex. . . . The charting of areas in terms of poorly defined and variable characters, in the hope that future physiological studies may some time reveal their significance, has contributed nothing to knowledge of cortical organization and gives no promise of better achievement in the future. If architectonic studies are to have value,

can be, then, no objection on grounds of anatomy to the physiological delimitation of the motor cortex, for just as the anterior limits of the relevant cortical layers in areas 4 and 6 (FA and FB) merge gradually into the changed conditions characteristic of areas lying anterior to them, so does the excitable cortex show a less than "hair-sharp" anterior border. The behaviour of the anterior part of the motor cortex is what its structure would lead us to expect of it.

(2) A physiological objection to the conception of the motor cortex here maintained might be urged if it could be shown that within its boundaries the presence of two distinct physiological mechanisms could be demonstrated. If, for example, it were found that the motor responses elicitable —under standard conditions—by stimulation of area 4 (FA) differ qualitatively from those resulting from stimulation of area 6 (FB) under comparable conditions, it could then be proposed that the Betz-cell-bearing area 4 (FAγ) is a physiological unit and that area 6 is another: then the names "motor" and "premotor" respectively applied to them by Fulton and his co-workers might express a physiological truth. On this point we have evidence from two main sources, the results of which appear at first sight to be in direct and complete conflict. The first source we find in the studies, already referred to, of Leyton and Sherrington in anthropoids and of Penfield and Boldrey in man. *In these we find no trace of any such dual mechanism within the motor cortex.* As the stimulating electrode passes anteriorly across the cortex of area 4 (FA) on to that of area 6 (FB) the character of the motor responses and the strength of stimulus necessary to evoke them show no change whatever except at the anterior fringe. The responses do not follow "the cytoarchitectural pattern," and we pass from excitable to silent cortex. For man and anthropoids, therefore, the two statements cited from Fulton (p. 434) in respect of these types appear quite without foundation. Stimulation experiments in them have provided no indication of the presence of a "premotor cortex" with functions qualitatively different from those of his "histologically defined" motor cortex, *i.e.*, area 4.

they must be based upon an adequate sample of the population and must employ a precision of descriptive method which has not been approached in existing studies."

It is only when we turn to the second source, the *cercopithecus* and *macacus* physiology of the Vogts and of Fulton and his co-workers, that evidence purporting to differentiate the reactions of areas 4 and 6 is submitted. In this body of observations we find it stated that as the stimulating electrode passes from area 4 to area 6 the threshold of excitability rises suddenly, and with equal suddenness motor responses of an unequivocally different order appear. For the Vogts, this physiological change has the same "hair-sharp" suddenness that they postulate for cytoarchitectonic borders.

To appreciate fully the basis of this claim it is necessary that we should be quite clear as to what are the qualities of the responses evoked from the motor cortex of Leyton and Sherrington, and the interested reader may be strongly urged to study for himself the relevant chapters in Leyton and Sherrington's classic paper.

They provide a list of over 500 movements observed by them on stimulation of the motor cortex. Each *threshold* stimulus applied for two seconds tends to give a sequence of simple movements, their first, second, third and fourth movements. The first is called the primary movement and it may be followed by one or more secondary movements. If stimulation be strengthened or prolonged, a definite "march" of movements occurs and this may issue in an epileptiform convulsion that persists after cessation of stimulation. Further, movements of all segments of the limbs, proximal as well as distal, and of all parts of the trunk are to be seen, and no movement of the skeletal musculature is unrepresented (save eye movements as primary movements). The nature of the response varies according to various named factors, amongst which the most important in our present connection are stimulation strength and duration. As these are raised, the responses become more widespread and therefore complex, and may, as we have seen, assume the characters of a Jacksonian fit.[1]

Before proceeding to summarize the evidence derived from *macacus* and *cercopithecus*, we may recall that in these

[1] A new light upon the form and significance of motor responses evocable from the cortex by electrical stimulation has been thrown by observations of Murphy and Gellhorn (*Arch. Neurol. Psychiat.*, 1919-45, 54, 256).

studies entire reliance is placed upon the areal chart of C. and O. Vogt. It is clear that conclusions based upon an anatomical foundation so largely uncertain must be taken with reserve.

In contrasting the differences between the motor responses evocable from areas 4 and 6 respectively, Bucy (1933) summarizes area 4 responses as follows: (i) they consist in discrete sustained responses involving small muscle groups, usually distal limb muscles rather than proximal; (ii) if stimulation be strengthened and prolonged the responses are more widespread, may be rhythmic and may issue in epileptiform after-discharge; (iii) with minimal stimuli the cortex anterior to a line from 5 to 7 mm. in front of and parallel with the fissure of Rolando is inexcitable. This line is said to correspond accurately with Vogts' line of division between areas 4 and 6. To demonstrate excitability in area 6 it is necessary to raise the strength of stimulation. When this is done motor responses are obtainable from the posterior part of area 6. With threshold stimuli these resemble the responses obtained from area 4, though the localization of the movements is said to be "less discrete." With stronger stimuli "an entirely different type of movement" is obtained, consisting of rhythmic and progressive movements. The last named are obtained with maximal stimuli and are so-called because they show after-discharge. If the cortex along the line assumed from the map to separate areas 4 and 6 be incised, no responses are any longer obtained from area 6 to near-threshold stimuli, but with maximal stimuli diminished rhythmic and progressive movements may still be obtained.

From these observations the following conclusions have been drawn: (i) The premotor cortex represents a motor mechanism with functions other than those of area 4; (ii) the disappearance of simple segmental movements on stimulation of area 6, when a cut separates it from area 4, shows that the impulses engendered in the former normally travel backwards through the cortex to the giant cells of Betz in area 4, and exciting these cells give rise to motor impulses which descend the pyramidal tract; (iii) the persistence of rhythmic and progressive movements when a

cut separates areas 4 and 6 shows that the latter has its own long projection tract distinct from the pyramidal tract; but (iv) the diminution in these movements in these circumstances show that some of the impulses responsible must also travel back to the Betz cells and descend thence by the pyramidal tract.

Various comments occur to the reader of this interpretation. It is difficult to ascertain in what consists this alleged *qualitative* difference between the reactions evocable from area 4 and some of those obtained from area 6. The latter do not seem to differ essentially from those we find when area 4 is *maximally* stimulated: namely, widespread movements with after-discharge that may issue in an epileptiform convulsion. On this point, also, Horsley, in the lecture already cited, has a pertinent comment to make: "It should not, in my opinion, be assumed that the effect of a minimal stimulus, evoking, as it often does, but a single movement of a single segment of a limb, is a criterion of all that is represented—that is, within that portion of the cortex cerebri."

It seems that as the anterior limits of the motor cortex are reached, the threshold of excitability rises, though it may be lowered even here by "facilitation," and at this previously inexcitable fringe, increased stimulation strength and duration will serve to evoke the simple segmental movements described by Bucy (and earlier described by C. and O. Vogt). With still stronger stimuli more extensive and longer-lasting movements appear and show after-discharge, and finally large fields of the musculature can be thrown into action. That some of this motor activity may be due to spread of current to posteriorly-lying cortex seems likely from the described effects of cutting a trench between areas 4 and 6. We have indeed seen in Foerster's cortical stimulation studies in man (1931) what very wide regions of the cerebral cortex can be made to yield movements on maximal stimulation, but to say that all the movements obtained in these circumstances indicate a normal motor function of the cortical regions stimulated would not be justified, and, indeed, the more careful exploration of the cortex by Penfield and Boldrey has shown that Foerster's

findings cannot be accepted. In this supposed selective excitability of the premotor cortex with its qualitatively distinct motor responses, therefore, it seems far more likely that we are seeing the results of the maximal stimulation of the *relatively* inexcitable anterior fringe of the motor cortex that lies in area 6 (FB), together with effects due to spread of current through the cortex to area 4. *All that can be elicited from this supposed premotor cortex can also be elicited from the rest of the motor cortex if this be sufficiently strongly stimulated.* It is interesting to note that the barbiturate anæsthetics are said totally to destroy the excitability of the premotor cortex, light ether anæsthesia (used by Leyton and Sherrington and by Bucy) is less depressant, but Penfield and Boldrey's stimulations were carried out in man under local anæsthesia, so that no question of any depression of cortical activity could arise. Yet under these favourable circumstances, these observers detected no trace of a physiologically distinct premotor mechanism.

Therefore, cortical stimulation experiments may be said to provide no satisfactory evidence of any division of the physiologically delimited motor cortex into two separable components. *The motor cortex as far as its activities can be displayed by this method is one and indivisible.* The cortex lying anterior to it appears electrically inexcitable.

Further evidence of the qualitative differences in function between the cortex of area 4 and that of area 6 is said to be provided by isolated ablations of these two areas, but the conflict of evidence here is so considerable that no conclusions can be drawn from these experiments. Thus area 4 ablations are said to provide hemiparesis, most marked in the distal limb segments, transient depression of tendon-jerks and transient flaccidity. In some experiments later increase in tendon-jerks and some hypertonus are recorded. Area 6 ablations are in some accounts said to produce marked spasticity, hemiparesis and apraxia (Fulton, 1935), but in other accounts (Fulton, Jacobsen and Kennard, 1932) these ablations were said not to lead to pronounced hypertonia. Repeating these experiments, Denny-Brown and Botterell (1936) found after area 4 ablations in *macacus* the type of hemiplegia familiar to clinicians, flaccid at first

not strictly comparable, the erroneous conclusion is reached that qualitative differences obtain between them, and thus the preconceived notion that the Betz cell is a specific entity *obtains a fallacious confirmation.*

In Leyton and Sherrington's and in Penfield and Boldrey's observations this error was avoided, and thus no evidence *of a dual cortical mechanism in areas 4 and 6 was obtained.*

It appears, also, that the motor cortex is not co-extensive with a cortical "area," a result that need not surprise us when we realize the true nature of cortical areas. *It seems* that the true correlation of function and structure here is between motor functions and the large pyramidal cells of layer V in areas FA and FB. In an earlier paper (1935) the present writer submitted that the motor cortex is not co-extensive with area 4, and drew from Foerster (1936) the protest that "the opinion has recently been expressed that the different cytoarchitectonic and myeloarchitectonic structure of these areas were merely anatomical details without physiological significance," but it is now clear that he was correlating function, not with structure, but with maps, and we see that applied cytoarchitectonics are wandering from the realities of anatomy. Economo and Koskinas have clearly pointed out the limitations and the nature of the areal map, but for C. and O. Vogt, as for Foerster, their cortical maps are precise guides of universal validity for every component of every cortical field in every individual brain.

These maps do not possess a factual accuracy of this high order, *and it is unthinkable that they should do so.* They cannot be treated as though they were mariner's charts which record the precise and unchanging form and extent *of individual concrete structures. Yet this is how* they are being increasingly treated, and applied cyto-architectonics are thus ceasing to provide the basis of a *scientific correlation of function and structure. Perhaps the* superlative example of this is Foerster's map of cortical areas in man, which is no more than a *cercopithecus* map of *uncertain accuracy redrawn upon a diagram of* the human brain. It is not the record of any human cytological studies, and the arbitrary process of its production is spoken of as "*homologizing the map for man.*" It would be difficult

to conceive of a chart more remote from the realities of the structures it purports to represent.

IV.—The Betz Cells, the Motor Cortex and the Origin of the Pyramidal Tract

"*Ebenso wie Cajal möchten wir ebenfalls annehmen, dass die grossen Pyramidenzellen und Riesenzellen der IIIc und V neben den Betzschen Kolossalzellen auch als Ursprungszellen der Willkürbewegungen und der Pyramidenbahn sind und das diese verschiedene Zellen also nicht anderes als durch ihre Grösse unterschiedene Individuen ein und derselben Zellart sind, deren Zellgrösse jedoch gewissermassen in umgekehrten Verhältnis zur Feinheit und Individualisierung der ausgelösten Bewegung steht.*"—Economo und Koskinas, "Die Cytoarchitektonik der Hirnrinde des erwachsenen Menschen," 1925, p. 290.

The conclusions that have been submitted from the available facts concerning the anatomical status of the Betz cell, in relation to other pyramidal cells and to the motor cortex, have prepared us for the probability that the pyramidal tract,[1] indeed, the entire category of upper motor neurones, as this term is commonly understood, arises from the large pyramidal cells and the simple giant cells of cortical layer V within area FA and the adjacent part of FB as well as from the giant cells of Betz. This is explicitly the view taken by Economo and Koskinas, and they portray on the surface of the cerebral cortex what they believe to be the cortical region corresponding to the field of origin of the fibres. Their diagram is here reproduced (Fig. 15).

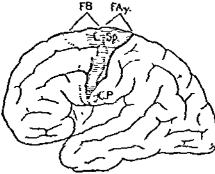


Fig. 15

Economo and Koskinas's Fig. 87 (p. 185) representing the presumed cortical field of origin of the corticospinal (pyramidal) and cortico-pontine fibres.

[1] The pyramidal tract comprises all the corticospinal fibres, and these fibres alone. As far as is known these all traverse the medullary pyramid. Above this level they are not wholly segregated, and it is possible that in the spinal cord this may also be true of them, but in the medullary pyramid nothing is known of any admixture of other than corticospinal fibres.

In citing authorities, however, we must beware of laying too much emphasis upon opinions that do not arise directly and necessarily from their observations, and it may be asked whether cytoarchitectonic studies can provide a conclusive answer to the question of the exact origin of the pyramidal tract. This at least we may say, that these studies show the close relationship between the three categories of pyramidal cells named above, and provide no ground for an exclusive attribution to the Betz cells of the origin of the pyramidal tract. The distribution of the Betz cells of itself affords strong evidence against such an attribution, for no less than 75 per cent. of them are found in the "leg and trunk areas" of the motor cortex, the extensive representation of the upper limb movement contains only 19 per cent., and the movements of the head, neck and face regions only 6 per cent. (Lassek, 1940) (see Fig. 14).

It is therefore incredible that the giant cells of Betz should give rise to all the long projection fibres serving the motor cortex and comprising the pyramidal tract and the shorter path to the brain-stem motor nuclei. Even if we consider the cortical representation of upper limb movements alone, we know that the region concerned contains a relatively small proportion of the Betz cells, but a very large number of simple giant and of ordinary large pyramidal cells, and we cannot escape the inference that the axones of the two latter groups must play a part in the motor functions of this region and contribute to its corticospinal projection. If, as has been stated, the ratio of the Betz cells to pyramidal fibres is as 1 : 40, how much greater is the discrepancy of numbers when we include the projection fibres to the brain-stem nuclei.

The recent fibre analyses of the pyramidal tract (Häggqvist, 1937; Lassek and Rasmussen, 1939; Lassek, 1942 (*a*)), seem to confirm the inadequacy of the Betz cells, numerically, to provide all the axones of the pyramidal tract even when due allowance is made for the difficulty in the precise identification of the Betz cell, and even if we double the largest current estimate and make the total 60,000 Betz cells. Lassek and Weil's (1929) original count gave 250,000 pyramidal fibres in the cervical pyramidal

tract, but later counts with more refined staining methods have given considerably larger figures. Lassek and Rasmussen (1939) give one million in man, and in a more recent count still Lassek (1942 (*a*)), finds in two young adults approximately 750,000 fibres. Still other interesting details have emerged from these studies. Thus, Häggqvist finds that the largest pyramidal fibres arise in the "leg area": that is, where the Betz cells are largest, the smallest fibres arising at the other extremity of the motor cortex where the Betz cells are smallest and fewest. He gives the range of fibre diameters as from 3 to 21 μ, five-sixths of the total being of the smallest calibre, and these he concludes to arise outside area 4. Lassek and Rasmussen, and Lassek (*loc. cit.*) find the pyramidal tract mainly composed of fine calibre fibres, only 4 per cent. having a diameter of more than 10 μ. Lassek classifies these fibres into four groups: small fibres of from 1 to 4 μ, medium fibres of from 5 to 10 μ, and large fibres of from 11 to 20 μ. Of the total, 89·57 per cent. are small, 8·7 per cent. medium and only 1·73 per cent. large. Over half the total were only 1 μ in diameter. Further, of the total, no less than 39 per cent. were non-medullated. Ranson (1913) and Wheelis and McKibben (1932) had previously reported the presence of non-medullated fibres in the pyramidal tract. The recognition of these non-medullated fibres has made possible more accurate fibre counts than heretofore.

From these findings certain inferences may be made. The pyramidal tract must be a slowly conducting path, since conduction rate increases with fibre diameter, as indicated in the writer's earlier review on cutaneous sensibility (1942). Therefore the pyramidal tract cannot be the "fast-train" pathway to the lower motor neurone postulated by Foerster (1931). Moreover, it seems unlikely that the giant cells of Betz can be responsible for the vast number of tiny non-medullated fibres of which the pyramidal tract is seen to be partly composed. It is probable that they provide the small percentage of large fibres.

There is still another method of approach to the problem. If all the pyramidal fibres arise from Betz cells in area 4, ablation of this area should produce total degeneration of

the pyramidal tract. Yet it has long been known that this does not ensue. Monakow (1915) pointed out that it required total destruction of the hemisphere to cause total loss of pyramidal fibres, and Schröder (1914) reported that loss of all Betz cells left the pyramidal tract apparently intact. Lassek (1942 (*c*)) performed cortical ablations in six monkeys, allowed periods from nine to eighteen weeks for degeneration to ensue before destroying the animals. After ablation of area 4, from 60 to 75 per cent. of pyramidal fibres remained intact, and even more extensive ablations left 50 per cent. of the fibres intact. Häggqvist (1937) found that four-fifths of the pyramidal fibres survived motor cortex ablation, the missing one-fifth being the largest fibres.

We are thus brought back to a consideration of the value of the method of reactionary chromatolysis, originally used by Holmes and Page May, and the original basis of the hypothesis that Betz cells alone give rise to pyramidal fibres.

It may be stated at once that we yet lack any final conclusive and positive demonstration that division of the axone does not invariably lead to retrograde degeneration of the cell of origin, but there is strong evidence that it does not. Thus, Tower (1940) found after division of the medullary pyramid that the pyramidal fibres were intact at pontine level above the section, while Davison (1937), in cases of thrombosis of the anterior spinal artery in man at medullary level, found that pyramidal fibre degeneration, proximal to the complete demyelinization of the pyramid at the lesion, did not even reach the pontine level where the fibres were all intact. If, then, both in monkey and in man, division of the pyramid does not cause degeneration of the fibres proximally, it would be remarkable if all the cells of origin of the fibres underwent reactionary chromatolysis. Further, Levin and Bradford's finding that 20 per cent. of the Betz cells remain intact after division of the cervical pyramidal tract is significant and suggests that even these large cells do not all undergo retrograde change.

Lassek's most recent study (1942 (*d*)) still leaves the question unanswered. He divided the pyramidal tract in the first cervical segment in the monkey, and found that

while the proximal parts of the severed fibres showed no degeneration, yet the Betz cells of area 4 did undergo retrograde degeneration and disappeared. He supposes that what has happened to them is that they have not fully degenerated, but that they have merely lost their Nissl substance and have shrunk so as to become undistinguishable from the numerous surrounding large pyramidal cells. These having no Nissl granules to lose do not change their appearance, and thus a fallacious impression is gained from the study of Nissl sections. Such a view scarcely accords with the finding of Holmes and Page May that all stages of degeneration can be seen in the Betz cells after pyramidal section, together with evidence of neuronophagia, and it seems, therefore, that the observations of these pioneer workers still stand uncontroverted. Nevertheless, the weight of evidence from many sources outweighs, it is reasonable to submit, any inferences we may draw from the method of retrograde degeneration. There are some three-quarters of a million pyramidal fibres to be accounted for, many of them fine and unmedullated, and 30,000 Betz cells cannot account for them. Possibly, quantitative studies of Nissl sections, *i.e.*, counts of the pyramidal cells in layer V of the relevant region before and after pyramidal section, might throw more light on the matter. Possibly, too, we are asking of the Nissl staining method more than it is capable of telling us.

In conclusion, therefore, both anatomical and physiological evidence points to the conclusion that in layer V (possibly also in layer IIIc) of the cerebral cortex we have a group of large pyramidal cells which include the giant cells of Betz, the simple giant cells and the large ordinary pyramidal cells, and that the axones of this group subserve the function of a projection system for the motor cortex. The cortical region in which these cells are found, and therefore the region from which this pyramidal projection system arises, includes the whole of area 4 (FA) and the posterior adjacent part of area 6 (FB). These cells and their axones constitute an anatomical unit performing a unitary function. Nevertheless, in spite of the compelling facts of anatomy on which these conclusions are based, we still find wide

expression of the view that the Betz cell is the sole cell of origin of the pyramidal tract, and that all corticospinal fibres arising in the Betz-cell-free part of area 4 (FA) and in area 6 (FB) are not pyramidal fibres, but belong to a special extrapyramidal tract subserving an anatomically and physiologically distinct "premotor" cortex. When we seek the basis for this proposed division of corticospinal fibres, we find that it does not necessarily arise from any recorded facts of observation, but from the hypothesis which runs as a repetitive theme through so much recent literature on the subject that the Betz cell is a specific morphological and physiological entity in a category by itself. Into what difficulties this assumption leads us becomes increasingly apparent as we follow it to its logical conclusion.

These difficulties began to appear when it was found that corticospinal fibres arise from area 6 in *macacus*. Thus, Kennard (1935) noted Marchi degenerations in the pyramidal tracts after ablations of area 6, while Hoff and Hoff (1934) and Hoff (1935) detected degeneration of the synaptic terminals of corticospinal fibres in the grey matter of the spinal cord after ablations of the same area, as well as after ablation of area 4 alone.

Kennard found that Marchi degeneration in the crossed and uncrossed (ventral and lateral) pyramidal tracts after ablation of area 6 were to be found uniformly scattered throughout these tracts. They did not form a special tract, but mingled with the pyramidal fibres. Her only reason for regarding these degenerated fibres as extrapyramidal was that they arose in area 6. They were therefore excluded *ex hypothesi* from being pyramidal fibres, and for no scientific reason.

In this way the "histologically defined motor cortex" of Fulton became endowed with its own pyramidal projection system arising in area 4, and the premotor cortex with a separate projection system arising in area 6. Both systems "followed the anatomic course of the true pyramidal pathways," but they were different merely because they arose in different cortical areas. After ablation of area 4 the numbers of these degenerated fibres in the pyramidal tracts was very much greater than after area 6 ablations.

Hoff and Hoff approached the problem in a somewhat different way. The results of Marchi degeneration studied after division of the corticospinal tract having given inconclusive results in the hands of very numerous observers, they took advantage of the fact that after such division the synaptic terminals of these fibres ("boutons terminaux," "Endfusse") degenerate rapidly. Within a few days they lose their normal loop-like appearance and become easily distinguishable granular masses lying round cells in the grey matter of the spinal cord.

These degenerated terminals are to be seen at the base of the dorsal horns of the grey matter and also more ventrally in the mid region of the grey matter and in the basal parts of the ventral horns.

These abnormal appearances were found to follow (*a*) ablation of area 4; (*b*) ablation of area 6; and (*c*) the cutting of an incision between areas 4 and 6. In their first paper Hoff and Hoff concluded that areas 4 and 6 both contribute to the pyramidal tract, and from the fact that a trench between these areas also leads to terminal degeneration they conclude that some of the projection fibres from area 6 run backwards into area 4 before turning deeply into the white matter. In a second paper, however, Hoff (1935) somewhat added to these conclusions by expressing the view that two groups of projection fibres are in question, a group from area 4 and another group from area 6. Thus the facts are forced into line with the hypothesis that there are pyramidal and extrapyramidal corticospinal projection tracts.

Yet the facts of observation are the same in both series of experiments, and it is not clear that any conclusion can be drawn from the second that is not inherent in the first. Fulton, however, suggests (1938) that there are differences in the distribution of the degenerated terminals within the grey matter according to whether the fibres bearing the terminals arise in area 4 or in area 6. There is nothing in the charts given by Hoff in either of the two relevant papers to bear out this contention. Therefore, these observations prove no more than that corticospinal fibres arising with area 4 and the adjacent posterior part of area 6 run together in the

pyramidal tract and end in the grey matter of the spinal cord. Of the existence of two anatomically and physiologically distinct projection systems they provide no evidence.

There is, on the other hand, some experimental evidence to show that the fibres arising from the relevant cells of the motor cortex and travelling in the pyramid of the medulla and pyramidal tracts of the spinal cord are all of one physiological category and do not subserve two distinct cortical motor mechanisms of different function. Tower (1940) has found that section of the pyramid in the medulla of the monkey produces a hemiplegia in which the "positive" element, so characteristic of residual hemiplegia in the human subject, is absent: that is, there is no spasticity. This finding cannot perhaps yet be regarded as wholly confirmed, because Marshall (1934, 1935) finds in the cat that there is some evidence of extensor hypertonus, but the absence of hypertonus appears to have been complete in Tower's monkeys. Now, it has been claimed that area 6 ablations of the cortex produce a notable contralateral hypertonus of the limb musculature, and even if we do not accept that hypertonus is wholly absent after area 4 ablations, it does appear that ablations of the anterior part of the physiologically delimited motor cortex where this lies in area 6 are associated with a definitely greater degree of hypertonus than in the case of ablations restricted to the posterior part of the motor cortex. How this is to be accounted for will be discussed subsequently, but it may here be said that Fulton and his co-workers interpret the development of this hypertonus as due to the interruption of impulses normally arising in the cells of premotor cortex and acting upon lower lying motor mechanisms. On this hypothesis, the residual spastic hemiplegia is the result of two factors: (i) loss of voluntary movements directly due to the destruction of the pyramidal tract arising in the Betz cells of area 4, and (ii) increase of tonic reflex mechanism activity due to its release from the control of the premotor cortex when the extrapyramidal projection tract from this cortex (*i.e.*, area 6) is destroyed by the capsular lesion that interrupts both pyramidal and extrapyramidal tracts. The view that the cerebral lesion underlying a spastic residual

hemiplegia might upon analysis be found to have two components, namely, a negative lesion of the corticospinal tract, and also one of another descending path from the cortex (though not necessarily a corticospinal path), was expressed a number of years ago by the present writer (1919), and this is, in fact, the view adopted by Fulton and his co-workers, with the difference that for them this second descending path is the extrapyramidal corticospinal path from the premotor cortex of area 6.

But it is this difference, this identification of the second path with the projection system of a supposed premotor cortical mechanism, that creates an insuperable difficulty, for if this system runs with the pyramidal path through the medulla and also in the pyramidal tracts of the cord, it also must be interrupted by a section of the medullary pyramid and therefore, *ex hypothesi*, section of the pyramid should produce the same spastic hemiplegia as results from the ordinary lesion in the internal capsule that underlies the familiar human hemiplegia. But, according to Tower, this is not what happens. The hemiplegia thus produced is flaccid, and therefore either there has been no section of an extrapyramidal path from the premotor cortex, or, if there has been, then this path cannot have the specific functions attributed to it in Fulton's hypothesis.

This vital flaw in the hypothesis has not escaped the notice of Ranson (1936) who, in a discussion on the projection tracts of areas 4 and 6, pointed out that according to some current views of the premotor cortex, section of the pyramid should produce spastic hemiplegia.

A final conclusion on this point must await further investigation of the effects of isolated section of the pyramidal tract, though if the results of Tower's experiments are accepted they entirely rule out the view that the pyramid and pyramidal tract contain fibres of two separate corticospinal projection systems, motor and premotor, each having distinct and quite different functions.

It yet remains possible, however, that the spastic residual hemiplegia is the fruit of a double lesion, but that the path, the interruption of which adds the component of spasticity to the hemiplegia, although cortical in origin, does not

arise exclusively in the cells within area 6, and that it is a short path going to subcortical centres and not to the *spinal cord. The point will be referred to subsequently.*

V.—Some Considerations on the Functions of the Motor Cortex

"*In the course of our work we have frequently had occasion to notice the unscientific process of multiplying existences beyond what are really needful to describe phenomena. The canon of inference which forbids this is one of the most important in the whole field of logical thought. It has been very concisely expressed by William of Occam in the maxim: Entia non sunt multiplicanda præter necessitatem. . . . Sir William Hamilton expresses Occam's canon in the more complete and adequate form: Neither more, nor more onerous, causes are to be assumed than are necessary to account for the phenomena.*"—Karl Pearson, "The Grammar of Science," Part 1, Third Edition, 1911.

In our consideration of available facts of observation as to the nature of the giant cell of Betz, the origin of the pyramidal tract and the anatomical substratum of the motor cortex, we have seen that a large body of hypothesis has been formulated from the interpretation, and upon occasion from the probable misinterpretation, of these facts. On the one hand we have the view advanced by Leyton and Sherrington which, containing no elements in conflict with the facts of anatomy, and no superfluous hypotheses, presents the motor cortex as co-extensive with the excitable frontal cortex and as a single indivisible mechanism physiologically considered. For an account of its functions viewed as a whole the reader must be referred to the original paper, but here we need only point out that the authors emphasize the highly co-ordinated nature of even the simplest and most restricted movement evoked by cortical stimulation, and the facility with which the motor cortex welds these fragments into complex movement combinations and sequences that are "eloquent of purpose." Nothing was found by these observers calling for any subdivision of the excitable cortex into separable anatomical or physiological components, nor has the later work of Penfield and Boldrey on the human cortex yielded any new fact necessitating any modification of the observations or deductions of Leyton and Sherrington.

On the other hand, we have another view on the matter, that associated with the name of Fulton and his collaborators, which from observations upon the lower apes has postulated a highly complex dual organization of the excitable cortex.

More than this, it rejects one of the most firmly based conclusions of the work of Leyton and Sherrington, and that of Hughlings Jackson in clinical neurology, namely, the doctrine of the cortical representation of movements, and postulates that in the "histologically defined" motor cortex, *i.e.*, area 4, it is not movements but individual muscles that are represented. Thus, Fulton states :

> "There has been a good deal of academic discussion as to whether individual muscles are represented in the motor cortex, or merely movements. Sherrington once said [1] that the central nervous system 'functions' in terms of movement rather than in terms of muscles, and the great neurologist, Hughlings Jackson, argued from his studies of epileptic seizures, that movements rather than single muscles find representation in the cerebral cortex : from this he argued that specific movements are impaired following cortical lesions, rather than specific muscles. Movements, *i.e.*, highly organized patterns of response, are indeed represented in the cortex as we shall see later, but in so far as the motor area is concerned, I would urge that the representation is of muscles rather than of movements. By means of this final common pathway from the cerebral mantle, over which travel highly organized integrations, individual muscles may be thrown into action in appropriate combination and sequence. By discrete stimulation of Betz cells single muscles, indeed small parts of a given muscle, can be thrown into activity. From this fact I regard it as proper to speak of a muscle having representation in the motor area, movements having representation in the larger cerebral organization of the frontal lobe."—(Hektoen Lecture, 1936.)

This is strange reading when we remember that reciprocal innervation obtains in every movement elicited by cortical stimulation and that in man the paralysis of a muscle as such is never seen in cerebral lesions, but only paralysis of movements. It would not be germane to our purpose to

[1] Chapter VIII of Sherrington's "Integrative Action of the Nervous System" is devoted to the reactions elicitable from the motor cortex, and presents in detail the evidence upon which their status as co-ordinated movements is accepted.

cite this lengthy and obscure passage were it not that it provides an illustration of the conclusions to which Fulton's hypothesis of a dual motor cortex inevitably leads him, and it is now the moment to view this hypothesis as a whole. Primarily based upon the assumptions that the giant cell of Betz is a specific cell with exclusive functions as the essential element in a "histologically defined" motor cortex, and that the pyramidal tract is composed solely of axones of these cells, it has to account for the fact that the cerebral cortex immediately anterior to the Betz cell area is also electrically excitable. The threshold of excitability of this region of cortex is high at its anterior limits, but, when a *threshold is obtainable here, stimulation at this strength* yields simple restricted movements not distinguishable from those obtained by threshold stimulation of the Betz cell area. Yet to strong stimuli it yields widespread movement sequences. These are then contrasted with the simple segmental movements elicited from the posterior part of the motor cortex by *threshold* stimuli, the fact that maximal stimuli applied here also yield widespread movement combinations and sequences with after-discharge being ignored. Thus, by comparing phenomena that are not strictly comparable and neglecting to compare those that are comparable, the conclusion is reached that there is a *qualitative* difference of function between the anterior and the posterior parts of the motor cortex. In this way it becomes possible to postulate the existence of two cortical motor mechanisms within the excitable region, a "histologically defined" motor cortex in area 4, and a "premotor cortex" in area 6. It now becomes necessary to provide each with its projection system. This is achieved by a fresh hypothesis, namely, that all corticospinal fibres arising in area 4 are to be called pyramidal, while all those that arise in area 6 are to be called the extrapyramidal projection system of the premotor cortex. The functions of the two systems thus *brought into being are different, destruction of the one*—area 4 and the pyramidal tract—produces simple hemiplegia without hypertonus, destruction of area 6 and its projection system leading to hypertonus.

So far we are dealing only with a multiplication of

hypotheses, each one arising, not so much out of the facts as out of its immediate predecessor in the chain, but at this juncture a direct conflict occurs, for *ex hypothesi*, section of the pyramid in the medulla must interrupt both of these projection tracts and should thus produce hemiplegia with spasticity. Yet, according to Tower's experiments, only a flaccid hemiplegia results from this lesion. No subsidiary hypothesis has yet been formulated to remove this difficulty.

The final link in the chain of hypothesis is provided by the last assumption that in the cortex of area 4 individual muscles are represented, while in area 6 movements are represented. Thus the contrast between the two mechanisms is brought to its logical conclusion.

In the final form the hypothesis takes we have a plethora of "more, and more onerous, causes" than are required to deal with the phenomena, with the addition of a direct conflict of hypothesis with phenomenon in the matter of the two projection tracts. It is impossible not to be reminded by this situation of Head's theory of the constitution of the afferent nervous system, in which the initial postulation of two unnecessary and unverified anatomical arrangements: the epicritic and protopathic systems, led to the inevitable formulation of a series of subsidiary hypotheses ; each called into being *ad hoc* to meet the difficulties created by the initial assumptions, yet failing in the end to provide a coherent hypothesis that generalized the facts of observation.

We may conclude, therefore, that the inferences drawn by Leyton and Sherrington as to the functions and constitution of the motor cortex alone provide a scientific generalization of the relevant phenomena : that is, the simplest possible satisfactory generalization. These inferences and those of Hughlings Jackson must still command our assent, which makes it impossible for us to accept the new and redundant hypotheses of Fulton and his collaborators, with which indeed they are in conflict. In short, the facts of observation do not require, and therefore do not justify, the postulation of the two mechanisms " histologically defined motor " and " premotor " of Fulton's hypothesis.

There remains for brief consideration one other feature of cortical motor function for which the clinical neurologist

yet awaits a satisfactory elucidation. Familiar with the clinical picture of residual spastic hemiplegia, as this results from a cerebral vascular lesion, he requires a conception of cortical motor function that will account, not only for the loss of movement that he observes, but also for the characteristic hypertonus and other positive phenomena in the clinical picture. Jackson has formulated the general principles that govern the appearance of "release" symptoms, but whether this release is—like the loss of movement—a result of loss of upper motor neurone function or requires the loss of function in some other neurone system remains problematical. We have seen how Fulton has attempted to provide the answer to this problem, and with what lack of success. The occasional occurrence of hemiplegia without concomitant positive symptoms is on record, sometimes with cortical, sometimes with more deeply seated cerebral lesions. Thus Davison and Bieber (1934) have described a series of cases of hemiplegia from vascular lesion, namely, middle cerebral artery thrombosis, in which, despite extensive damage to the "premotor" area (area 6) the hemiplegias remained flaccid throughout life. So far, then, human material has not provided an answer to this question. Many years ago (1919) the present writer was led to suggest that "from clinical and experimental sources *come several indications, as yet imperfectly understood,* that a pure cortical lesion of the pyramidal system often *does not produce spasticity as an accompaniment of the* loss of power. They suggest the possibility that in the cerebral lesion underlying, for example, a typical spastic residual hemiplegia, analysis may ultimately reveal a second component. That is, that in addition to a negative lesion of the corticospinal path, interruption of another descending path may be concerned in the production of spasticity. Such a path need not be cerebrospinal."

It may be worth while, therefore, to consider the relevant facts of anatomical and experimental observation to see whether they throw any light upon the dual symptomatology of what is known to the clinician as the upper motor neurone type of paralysis, of which hemiplegia with spasticity provides the most familiar example.

Let us attempt the task on the basis of the laminar physiology of the motor cortex already referred to. We have seen that in layer V of the motor cortex we have a large group of pyramidal cells, all of one " Zellart " and including the giant cells of Betz, the simple giant and the large pyramidal cells. This layer, or field, of cells coincides with the limits of the motor cortex and with the field of origin of the pyramidal tract. It is not unreasonable to assume that this group of cells and their axones belong to a unit of physiological function, the motor cortex. Dusser de Barenne's thermo-coagulation experiments, already referred to, afford some measure of support to this view in that—as far as they go—they seem to indicate that the cells of layer III play no significant rôle in this unit of function.

Let us also consider the possibility that the field of simple giant cells and of large pyramidal cells of layer III in area FA and the greater part—if not the whole—of Area FB, belong to another physiological unit. The extent of this unit, measured in terms of cortical areas, is greater than that of the relevant cells of layer V, for, as we have seen, the large pyramidal cells of layer III reach in area FB dimensions only second to those of the giant cells of Betz. We have no information whatever as to the nature of the projection system arising from this group of cells, but *no evidence that it is corticospinal*. We do know, however, that there are short projection tracts arising in areas 4 and 6 in monkeys. These include a precentropontine tract, corticorubral and corticonigral tracts (Levin, 1936) and corticotectal tracts (Beevor and Horsley, 1902).

It is possible that one or more of these short tracts may constitute the projection system of our group of cells in layer III of area FA and FB. These cells and their axones may thus be part of the system, a negative lesion of which permits the development of the positive symptoms of hemiplegia. The extension of this field of cells well into area FB, in which its focus may well lie, may account for the more marked degree of hypertonus that ensues when ablations encroach upon the region immediately anterior to the motor cortex. Thus we should have two physiological units, overlapping when considered in terms of cortical areas, but

not co-extensive: units, the presence of which might not only account for the dual symptomatology of residual upper motor neurone paralysis, but also in some degree for the striking and disconcerting disparities of observation that we find in the *macacus* experimental physiology of this region.

No one conscious of the almost unbelievably complex character of the neuronal connections in the cortex will speculate without diffidence on these problems, but the issue has been raised by the experimental studies referred to, though not solved by them, and therefore an alternative point of view—submitted only tentatively—may be justified.

It should, however, be emphasized that there is as yet no conclusive evidence that isolated interruption of the corticospinal projection system from the motor cortex is *not adequate to produce both the negative and the positive* symptoms of spastic residual paralysis from cerebral lesion in man, and dogmatic pronouncements to the contrary—based upon the dual hypothesis of Fulton—should be treated with reserve, and it is probable that all the *macacus* experimental work on this subject will demand repetition and confirmation before we shall be in a position to draw any conclusions from it.

VI.—General Conclusions

"*Es vielleicht doch ein Trugschluss ist, in den man gar zu leicht verfallt, wenn man im allgemeinen nach der Grösse der Zellen auch auf ihre Bedeutung und physiologische Dignität schliessen zu durfen glaubt.*"—Economo und Koskinas, "Die Cytoarchitektonik der Grosshirnrinde des erwachsenen Menschen," 1925.

"*In fact, it may be stated positively that not one character upon which parcellation of the cortex has been based has been shown to be specifically related to the functions ascribed to the area which it characterizes. Other factors than diversity of function may be responsible for structural differences.*"—Lashley and Clark (*loc. cit.*).

Perhaps the most important conclusion reached in this review is that the giant cells of Betz do not constitute a specific morphological and physiological category, standing apart from the other large pyramidal cells of cortical areas 4 and 6, or FA and FB. Physiological experiment has failed to show that these cells have exclusive functions not shared by other large pyramidal cells in layer V of these areas. On the contrary, all the evidence is that they do share their

functions with these cells. On histological grounds, Economo and Koskinas have come to the conclusion that the giant cells of Betz, the simple giant cells and the large pyramidal cells are of one " Zellart " and differ merely in their size. From their distribution, these observers conclude that the largest giant cells mediate the simple movements of the legs and trunk, and that the finer and more complex movements are subserved by the smallest giant cells and by the large pyramidal cells.

These conclusions make possible a return to realism in our consideration of the structure and functions of the motor cortex, and they clear away the edifice of hypothesis that has been built upon the initial assumption of the specificity of the giant cell of Betz.

It seems, then, that the anatomical basis of the physiologically delimited motor cortex includes as an essential element these three dimensional categories of cell : Betz cell, simple giant cell, large pyramidal cell, as they lie in cortical layer V within the boundaries of the cortical areas named 4 and 6 (or FA and FB). It is from these cells that arise the fibres of the upper motor neurone (corticospinal fibres of the pyramidal tract, and cortical fibres to the motor nuclei of the brain-stem), and the field of distribution of these cells is the field of origin of this category of fibres.

This brings us to the question of the relation of these structures to the familiar cortical areal map.

Reasons have been given for concluding that a correlation of a cortical function with a cortical " area " is not truly a correlation of function with structure. A cortical area is largely a convention, it is certainly not a structure ; indeed, it is no more than a two-dimensional representation that seeks to sum the conflicting claims of six independently varying cortical layers. Within a cortical area, one cortical lamina may undergo notable changes, while another lamina may extend unchanged into an adjacent area. Therefore, the correlation of cortical function with cortical structure must be a correlation with cells, fibres, and cell and fibre arrangements in the relevant lamina or laminæ, and in the particular case of the motor cortex it is a correlation with the large pyramidal cells, already defined, that lie in layer V

in cortical areas 4 and 6. The attempted correlation of *function with "area" is a misapplication of cortical* cytoarchitectonics and has proved misleading in this connection.

We have learned, also, that at any rate in man and the anthropoid apes, the motor cortex is one and indivisible and shows no evidence within its borders of the existence of two separate physiological mechanisms, and it merges anteriorly on silent cortex : that is, electrically inexcitable cortex.[1]

The projection tract of this cortex is the pyramidal tract together with the contingent of shorter cortical fibres that pass to the motor nerve nuclei of the brain-stem. The evidence submitted from experiments on *cercopithecus* and *macacus* to the effect that there are two separable motor mechanisms, a "histologically defined motor cortex" and a "premotor" cortex, is capable of a simpler interpretation and is primarily based upon the untenable hypothesis that the Betz cell is a specific entity.

This hypothesis of a dual cortical motor mechanism within the excitable frontal cortex recalls Head's theory of the afferent nervous system in which, also, two separate anatomical sensory mechanisms were postulated, and it seems highly probable that it is a figment of a comparable order.

Turning from this aspect of the subject to the correlation of Betz cells with pyramidal fibres and with the cortical projection fibres to the motor nuclei of the brain-stem, we find a striking discrepancy between the estimated totals of Betz cells with the numerical analyses of the pyramidal fibres, a discrepancy that must be much greater when we take the fibres to the brain-stem also into consideration. Even if we make the most generous allowance for the range of error in Betz cell enumeration inherent in the difficulties that the identification of these cells presents, the discrepancy remains quite remarkable. Further, the pyramidal tract appears as predominantly a fine fibre, and hence a slowly conducting path, and contains a considerable proportion

[1] The topographically separate excitable field for primary eye movements is a distinct anatomical mechanism with its own physiological properties.

of unmyelinated fibres. In short, it has become impossible to maintain that the Betz cells can provide any more than a proportion of the fibres that make up the pyramidal tract. The method of retrograde degeneration upon which the attribution of pyramidal fibre origin to the Betz cells rests is probably not valid for this purpose since we may not conclude that all the cells the axones of which are divided show reactionary changes.

The question of a consideration of cortical motor function in terms of cortical laminæ has also been raised, and it seems possible that in what we may call a laminar physiology we may find the solution of some of the outstanding obscurities of cortical function. In the present state of knowledge nothing definite can be said on this point.

In conclusion, in a recent review of the anatomy and physiology of cutaneous sensibility, the present writer (1942) referred to the tendency evident in the literature of the subject to postulate anatomical structures in accounting for the phenomena, without attempting to establish whether or not such structures were present, and it appeared in some notable instances that anatomical research had failed to demonstrate their presence. From what has been said in the present review, it is clear that this tendency is not confined to the literature of sensory function, but is much in evidence in current hypotheses of cortical motor function. Here it shows itself by the arbitrary creating of anatomical categories amongst cells and fibres, and the attribution to each of these of exclusive functions. This necessarily involves a multiplication of hypotheses to account for observed phenomena beyond what these require in their generalization. Some of these hypotheses are pure assumptions, others purport to flow from the facts but do not clearly do so. Thus, the current views on cortical motor function have been needlessly complicated and contain a large element of assumption that is not clearly submitted as such.

Accompanying this defect in logical thought, and therefore in scientific method, is the employment of a loose nomenclature : sometimes capable of more than one meaning, as in the current usages of the term "motor cortex"; sometimes having no single clear and unequivocal referent.

Of the latter type is the term "giant cell." For approximately seventy years we have taken it for granted that this term referred to a well-defined specific cell category, and we have *thus been led to attribute to it specific and exclusive* functions. Yet it has never been a term of precision and on examination is found incapable of being made so, since the structure to which it refers has no specific individuality of the kind postulated for it. When we consider the active and widespread pursuit of neurophysiology, seventy years is an overlong period for an assumption to have remained current without examination, and the reflection arises that perhaps in our haste to add to knowledge, we have sometimes neglected that "unresting contemplation of the facts of observation," and that periodical halting to examine our basic assumptions that are so essential to the building of a stable fabric of ordered knowledge.

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On the Mode of Representation of Movements in the Motor Cortex, with Special Reference to "Convulsions beginning Unilaterally" (Jackson)

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SYNOPSIS

I. Introduction.

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Chapter III

On the Mode of Representation of Movements in the Motor Cortex, with Special Reference to "Convulsions beginning Unilaterally" (Jackson).

I.—Introduction

For our knowledge of the topography and mode of representation of movements in the cerebral cortex we are jointly indebted to clinical and to experimental observations. Destroying or stimulating ("irritating") lesions of the cortex produced by the action of disease in man, and electrical stimulation and cortical ablation performed in apes and other animals by experimentalists, have been the sources of our information, and to these may be added the results of electrical stimulation of the human cortex carried out by surgeons in the course of surgical interventions on the brain.

It was reasoning from clinical observation that gave us the first inkling of a representation of movement and of a localization of function in the cerebral cortex, and the sequence of initial steps in the attainment of our present knowledge is to be found in summary in Schafer's (1900) "Textbook of Physiology," thus: "Previously to 1870 it was almost universally held that the cortex cerebri could not be excited artificially, that there was no localization of particular functions in particular parts, that the cortex must act for each and all of its functions as a whole, and that lesions of the cortex produce, according to their extent, only a general depression of the functions of the cerebrum without special symptoms of local paresis. This doctrine was supposed to be firmly established by the experiments of Flourens (1842) which led him to reject absolutely the localization of function which had been formulated, on altogether indifferent evidence, by the phrenologists, and it remained for many years in almost undisputed possession of the field. A notable exception had, however, to be made

after it had been shown, by the masterly researches of Broca (1861), that one important function of the cerebrum, that of producing articulate language, is intimately associated with the integrity of the posterior part of the third frontal convolution of the left hemisphere of the brain, and doubt had begun to be thrown on the doctrine, at least in its rigid acceptation, by Hughlings Jackson (1868), and by Bastian (1869), the former of whom was led somewhat later from the study of certain cases of epilepsy, following lesion of the brain in man, to the conclusion that the symptoms could best be explained by the assumption of functional localizations, the epileptiform contractions being regarded as the result of irritative lesions (1870). This was the condition of the subject when, in 1870, were published the experiments of Fritsch and Hitzig, which clearly showed that the doctrine of the non-excitability of the cortex was erroneous."

A study of Jackson's early papers reveals what strength of opposition his inferences encountered and how firmly rooted in the contemporary view was the notion that the cerebral convolutions were "for mentation" only.

The clinical neurologist, in studying the knowledge at our disposal as to the nature of the cortical representation of movements, cannot but be struck by the apparent unrelatedness of the two sources of our information on the subject. On the one hand, the literature of electrical stimulation of the cortex, both in apes and in man, presents the picture of a mosaic of excitable points each yielding its characteristic and circumscribed motor response. In the papers of Leyton and Sherrington (1917) and in those of Graham Brown (1912, 1915 (*a*), (*b*), (*c*)) he learns that the matter is indeed more complex than this summary statement implies, in that the excitable cortex shows certain marked features of instability; the response evoked from any given cortical point is often determined by precurrent stimulation of the same or of adjacent points, and a point which on one occasion yields a movement may on another be silent. This instability has been analysed by these observers into three factors named by them—*facilitation, deviation and reversal.* To these further reference will be made, but, nevertheless,

the broad impression left on the reader is of a pattern of discrete points each yielding on stimulation a small movement, or a sequence of small movements employing small numbers of muscles.

On the clinical side we have the phenomena of Jacksonian fits, or as Jackson named them, "convulsions beginning unilaterally." There appear to be three predominant foci in the motor cortex from which these almost invariably arise: they are the foci for movements of the thumb and index, the angle of the mouth and the hallux. All Jacksonian attacks seem to spread from these parts in an ordered "march" of convulsion that, as a rule, corresponds fairly closely with the topographical order of localization of movements of the cortex as this order has been revealed by experimental stimulation. Jackson speaks of these three cortical foci as "physiological fulminates," and there must be physiological properties inherent in them, and not shared in equal degree by other regions of this cortex, that lead them to react in this way to internal states of the cortex that can hardly be rigidly confined to them. As to what these properties may be, experimental cortical stimulation gives no clue and offers no explanation.

On the basis of his close study of these convulsions and of destroying lesions, Jackson put forward a conception of the mode of cortical representation of movements that at first sight makes no contact with the inferences as to this representation drawn by Leyton and Sherrington and other experimental physiologists, and as far as the present writer is aware no attempt has yet been made to achieve a synthesis of these two bodies of observation, clinical and experimental. Yet a comparative study seems clearly to show that in certain characteristics of cortical activity, as revealed by experiment, we have the very qualities generalized by Jackson's hypothesis. Therefore, a synthesis of these two approaches to the problem of the cortical representation of movements is long overdue, and is here attempted.

Perhaps one of the most striking features of the vast literature on the experimental physiology of the motor cortex of the past seventy years is that it has been largely anatomical in its outlook and inspiration, concerning itself

with the "where" rather than with the "how" of the cortical representation of movements. Apart from the papers of Graham Brown and Sherrington on facilitation, and the chapter on the functions of the motor cortex in Leyton and Sherrington's classic paper, physiological principles of representation have not greatly engaged the attention of any of those working on this subject. Hence, the original punctate localization theory of the pioneers still holds a precarious sway, despite a vague awareness of its inadequacy as a generalization of the facts.

II.—Jackson's Hypothesis of the Representation of Movements and the Punctate Localization Theory

The representation we are considering is one of movements and not one of parts. As Jackson pointed out, the cerebral cortex represents sensorimotor processes and can represent nothing else. In other words, the nervous substrata of processes are localized in the cortex, and not the performing parts themselves. Yet it is customary to speak of a representation of parts in the cortex, and provided that this usage is not literally intended it is convenient and lends itself to economy of expression. Nevertheless, it is clear from much current writing on the subject that the representation of parts is literally intended. Thus Woolsey, Marshall and Bard (1942) protest against the notion of an exclusive representation of functions in the cortex: a notion they erroneously attribute to Head as its original proposer, and believe that dermatomes are represented in the cortex. A representation of muscles is also assumed by Fulton (1938) and Foerster (1931). Yet, if we hold this view—if, for example, we hold that the hand is represented in the motor cortex—we have next to state what precisely of this structure is thus represented. Surely, not any one, or all, of its component tissues, for, apart from its functions as a motile part, the cortex may be said not to be interested in the hand. It is the motor performance of the hand that is relevant. In short, the cortex represents performances and not performing parts.

That muscles are not therein represented is illustrated

daily by every case of residual hemiparesis, where we may see the extensors of the wrist "paralysed" as prime movers in an attempted voluntary extension of the wrist, but powerfully active as synergists in every forceful grasping movement of the fist. Were a direct representation of muscles in question this familiar clinical phenomenon could not occur. Further, before proceeding to discuss Jackson's hypothesis some closer definition of the terms "represent" and "representation" may be useful. Both are in current use in physiological and clinical neurological literature. Yet it is clear that the process referred to by these terms may be thought of under different aspects and may thus come to mean different things to different men, according to the method of approach in question.

The early experimental workers on the cortex considered the functions of the excitable region in terms of visible motor performance, and this is still the aspect of these functions that presents itself to the clinical observer. The movements may be those evoked by electrical stimulation, by the action of disease processes on the cortex, or they may be the normal voluntary movements. From the study of the two former and their correlation with experimental excitation or local lesions of the cortex, it has been possible to localize the nervous mechanisms involved in any given movements, and thus such a movement came to be spoken of as localized or represented at some point of the motor cortex. It was further possible by anatomo-clinical correlations of this order, and also by experimental stimulation of the cortex, to formulate general principles of the plan of this representation, and of the mode in which the cortex initiates movements.

The word "representation" thus used is a general term for all those processes in the cortex by which these visible results are brought about, and this method of direct observation does not concern itself with the analysis of these processes, *e.g.*, conduction in the neurone and across synaptic junctions, the physical bases of facilitation, excitation, etc., and the term "representation" as thus employed subsumes all these processes. To the physiologist intent upon their analysis, this usage answers none of his questions, but there

is no reason why we should expect it to do so. The analysis of cortical function in terms of conduction, facilitation, inhibition, etc., deals with another aspect of the problem—an aspect complementary to that revealed by the method of direct observation. Not unnaturally, however, these two methods of approach tend to have their own special languages, and it is therefore essential in this attempted synthesis that Jackson's hypothesis should be expounded in an idiom intelligible to the modern reader. This somewhat lengthy digression is dictated by the objection that Jackson's use of the term "representation" has no meaning for the modern experimental student of motor cortical functions, and by the desire to show that these two methods of approach, the clinical and the electro-physiological, are of equal validity, and that each reveals one aspect of reality; or, in other words, that the two describe one series of happenings in two languages, neither of which is more, or less, scientific than the other.

(i) *Jackson's Hypothesis*[1]

In this the motor cortex is believed to represent all the movements which the individual is capable of initiating, a view that implies a distinct and separate representation for each of the almost innumerable purposive movements the individual acquires during the course of life, however little one of these may differ from another. Put in another way, we may say that there is a pattern of excitation for each movement. It follows that the leading motile parts, that is, those having the most numerous and the most varied movements, must have the most extensive representation in respect of these movements, while parts that have the fewest distinct movements (*e.g.*, the thoracic cage) will need in respect of them a correspondingly limited representation. In order of importance, Jackson names the leading parts as the thumb and index finger, the lower part of the face

[1] The most concise and detailed exposition of this hypothesis is to be found in Jackson's paper entitled "Some Implications of Dissolution of the Nervous System" ("Selected Writings," Vol. II, p. 29). It contains conclusive arguments against (i) a representation of muscles in the cortex, and (ii) the then—and still—current doctrine of a punctate localization in the cortex.

useful purpose without fixation of the wrist (and of parts further and further in automaticity according to the force required), we should *a priori* be sure that the centre discharged, although it might represent movements in which the thumb had the leading part, must represent also certain other movements of the forearm, upper arm, etc., which serve subordinately" ("Selected Writings," Vol. I, p. 69).

Hence, the "hand area," for example, is not merely the cortical region in which movements of the hand alone are represented, but one in which the movements represented are mainly and predominantly those of the hand. Conversely, this area is not the sole region of representation of hand movements, for these are represented subordinately throughout the motor cortex, the so-called "hand area" being simply the "yellow spot" of their representation. *Thus the motor cortex is to be conceived of, not as a mosaic of abrupt localizations, but as a complex pattern of overlapping and graded representations.* Jackson maintained that it is only on the basis of such a mode of representation that we can account for (i) the transience and narrow incidence of paralysis following local destroying lesions of the cortex and (ii) the widespread distribution of convulsion from local stimulating lesions.

After a local destroying lesion, the functions of the destroyed part are not "taken over" by other parts, and compensation is never absolutely complete (Jackson's law of compensation), but so numerous and extensive are the representations of movements of a given part that the loss is virtually concealed by the vast repertoire of movements, the cortical substrata of which are left intact. Thus, while routine clinical examination may fail to reveal deficit of movement in such a part as the hand and digits, the patient himself may yet remain aware of a permanent impoverishment of his range of movements, as revealed to him when he tries to write or to play a musical instrument.

On the other hand, such a plan of representation necessarily involves that a stimulating lesion of the cortex will release a widespread convulsion, even without there being any considerable or necessary spread of the excitatory process throughout the cortex. The two following citations

summarize Jackson's views: "It is obvious that the larger quantity of grey matter representing numerous different movements must be made up of a great number of different parts. Each movement, so far as it differs from all others, must have so far special representation in the nervous centres. Greater differentiation of function implies greater physical separation, however little different the movement may be from other movements, and however much it may be a reco-ordination of other movements. So far as there is a degree of independence of movement, so far there must be a degree of separateness of representation by different cells in the nervous centres. And yet, of course, the separation is not isolation; on the contrary, the greater the differentiation, the more complete the integration of the different elements, for they have to act together or in succession . . . any part, especially such a one as the hand, is represented in innumerable places" ("Selected Writings," Vol. I, p. 263). And again: "If any one part of the brain in this region (cortex) be destroyed, there is no obvious loss of movements, because the movements it represented are still represented in each neighbouring part, although in different degrees and orders. But for this very reason, if any *one* part be strongly *discharged*, vast numbers of movements are developed" (*loc. cit.*, p. 115).

At first sight such an hypothesis appears remote from anything that can be inferred from cortical stimulation experiments. These are thought (Fulton, 1938) to reveal "a mosaic of circumscribed foci" each subserving a small physiological unit of function. Jackson's hypothesis postulates a fabric of interwoven and graded representations.

In other terms, according to Jackson the cortical mechanism responsible for initiating the movements of a given part, such as the hand and digits, is not one part of a mosaic within which all the movements of that part are localized. The plan is one in which these movements are very widely localized. All normal movements necessarily involve wide fields of muscles, and no normal movements are narrowly confined to the muscles of a single part. In every normal movement-complex some one part is the leading part—the predominant component—and there are

numerous subordinate components. There must therefore be an infinite number of patterns of movement—and underlying them, patterns of excitation in the cortex. These patterns are spread out widely throughout the motor cortex and they overlap widely.

(ii) *The Punctate Localization Theory*

The notion of the motor cortex as a simple "mosaic," each item of which contains the nervous mechanism subserving a single restricted movement, has already been referred to. This was the notion of the original pioneers of experimental cortical stimulation, and by those who hold any doctrine of localization of function within the cortex it has never been explicitly rejected, as we may see from the writing of Leyton and Sherrington (1917), Fulton (1938), and Dusser de Barenne (1934). Nevertheless, the phenomena of cortical instability discovered by Graham Brown and Sherrington have rendered it difficult of acceptance in its original form. The facts of facilitation, deviation and reversal of response and that of extinction of response have been exemplified and discussed by Graham Brown (1915 (*a*), (*b*), (*c*)), by Sherrington and Graham Brown (1912) and by Leyton and Sherrington (1917), and the following brief summary may be given here.

Bubnoff and Heidenhain (1881) first noted that the electrical stimulation of a cortical point at brief intervals led to an increase in the motor response evocable from that point, and they also noted another fact of interest that has, as we shall see, its counterpart in the phenomena of the Jacksonian fit—namely, that antecedent cutaneous stimulation of the limb responding to cortical stimulation augments the response. Francois-Franck (cited by Schafer, 1900) made a similar observation. Studies by Graham Brown (1915 (*a*), (*b*), (*c*)), Graham Brown and Sherrington (1912) and Leyton and Sherrington (1917) have shown that a liminal stimulus of one second duration, repeated at one-second intervals, increases the excitability of the point stimulated, and also that of adjacent cortical points (secondary facilitation). This facilitation may show itself

by the appearance of response from a point not previously yielding one, or by an augmented response from a previously active point.

This procedure may also lead to an alteration—"deviation"—of the response previously obtained from a point adjacent to that subject to recurrent stimulation. The following striking deviation phenomenon may be cited from the paper of Leyton and Sherrington, and it shows how widely this change in cortical excitability may spread. "In a chimpanzee the following was noted. The lower limit of hand area was determined, care being taken to avoid as far as possible deviation of response by near precurrent stimulation of adjacent points. Similarly the upper limit of angle of mouth was delimited. Then the lower limit of hand area was obtained by stimulation in serial succession of a number of points descending in order from upper part of arm downward. The lower border of hand area as thus examined trespassed into face area according to the upper limit of the latter as demarcated previously. . . . Conversely, on determining the upper limit of angle of mouth area by following that area upwards along a series of points stimulated in it in turn, the upper limit trespassed over into hand area."

Comparable examples are given in this paper in which particular movements may be evoked from cortical points previously yielding other movements. Also, complete reversal of response may be evoked (Graham Brown and Sherrington, 1912).

These facilitation phenomena are most readily demonstrated within a given functional area, *e.g.*, within "hand" or "leg" areas, and less easily from one such area to another, but even these functional boundaries may be transgressed, as the example cited above clearly shows. Another feature of cortical instability has recently been revealed by Dusser de Barenne and McCulloch (1934, 1939) under the name of "extinction." Here, when an initial stimulus to a cortical point is repeated after an interval of one or more seconds (according to certain factors of stimulation strength, duration, etc., and degree of anæsthesia employed) the second stimulus may evoke a diminished response or there

may be complete extinction of response. There may also be an interplay of facilitation and extinction according to certain variable factors of procedure.

Still more recently, Dusser de Barenne, Garol and McCulloch (1941) have recorded a series of observations on the motor and sensory cortex of the chimpanzee that may lead to considerable modification of our views on the topography and organization of these functional regions, if further investigation confirms them. They claim that under the influence of secondary facilitation, motor responses may be obtained from a wider area of cortex, both pre-central and post-central than that indicated in the work of Leyton and Sherrington; in fact, from the entire "sensory cortex" as revealed by the strychninization method of Dusser de Barenne. Further, bounding this area anteriorly and posteriorly, and also within it, they report the presence of four zones of cortex, running coronally from vertex laterally across the cortex, stimulation of which inhibits the normal electrical activity of the cortex and also inhibits the appearance of motor responses from normally excitable areas. These findings probably are relevant to certain points discussed in this paper, *e.g.*, the sudden loss of power in a limb or limb segment in certain Jacksonian attacks, but they do not bear, as far as can be seen, on the general principles of cortical localization of movements as formulated by Jackson.

Summing up the results of experimental observation on cortical stimulation we find they come naturally under two headings: (i) electrical stimulation appears to "sample" the motor cortex, revealing "fragmentary reactions," but not clearly revealing the general design of the cortical representation of movements. The method by which these items of movement are evoked is so remote from anything normally obtaining that we cannot even be sure that what we see are in truth normal components—physiological units—of cortical function. It appears to be generally assumed that we are dealing with true units of function, not materially changed from the normal despite the abnormality of the method by which they are produced. It would be as reasonable to regard the more complex

phenomena of a Jacksonian convulsion as something "normal" evoked by the experimental hand of disease, yet, as Jackson has pointed out, such a convulsion is a gross disorder of *co-ordination of time*. That the item of movement evoked by a brief electrical stimulus to the cortex shows, as it invariably does, reciprocal innervation, indicates that some degree of co-ordinated activity has been revealed; but that we are looking at a normal unit of function, normally laid down as such in the cortex, we cannot be sure. Nevertheless it is on this foundation of a "discrete representation of small local items of movement, each highly co-ordinated with others yet separately elicitable," that Leyton and Sherrington develop their view as to the function of the motor cortex. They believe that "the individual movements, elicited by somewhat minutely localized stimulations, are, broadly speaking, fractional, in the sense that each, though co-ordinately executed, forms, so to speak, but a unitary part of some more complex act, that would, to attain its purpose, involve combinations of that unitary movement with others to make up a useful whole," and "the multiform combinations which these (units) assume under cortical reaction and the rich mutual associations of the cortical motor points which the physiological phenomena of "facilitation" and "deviation of response reveal" indicate that a building up of these units is a main cortical function.

(ii) This hypothesis, however, is rather complicated than completed by the presence of the two last-named phenomena. That they bespeak an instability of the cortex, a capacity for reacting to experience in other terms, is perhaps clear, but what is not clear is precisely how facilitation and deviation—occurring on the background of a punctate localization of units of movement, contribute to the synthesis of movements which is the main cortical function. That there is some obscurity about this is revealed by the further statement that the fixity of motor localizations indicated in their charts "is as regards minutiæ to some extent probably a temporary one, *i.e.*, obtained at the time of observation, but in our opinion might not be precisely the same were examination possible at a number of different times and in a number of different experiments . . . the

motor cortex is a labile organ." It would seem, therefore, that the apparent shifting of the localization of units of movement from point to point involved in deviation is not really accounted for, and this is evident in an observation of Dusser de Barenne (1933) in which he says that "even for the electrically excitable cortex itself there is evidence at present that the relations between the foci and the striped peripheral musculature are by no means so fixed and rigid as the classic localization theory asserts. These relations are on the contrary rather loose, being easily disturbed and broken down."

There is a prevailing element of the negative in these two last conclusions, and it is important to realize what they imply: they imply that there are no really fixed foci of localization, even of units of movement, in the cortex; that a cortical point that at a given moment represents (contains the pattern of excitation of) a given movement, may at another moment represent a different movement; and that but one movement is represented at a given point at a given moment. In other words, the anatomical and physiological nervous substrata of a given movement differ, from moment to moment. On this hypothesis no more can be said as to the significance of facilitation and deviation than that, as Dusser de Barenne remarks, they break down the relations between cortical foci and the musculature. But to say this is not to define their function, it is plainly to confess this function undiscovered.

In the most recent review of cortical motor function, Hines (1943) provides an admirable summary and critique of the vast mass of facts that experimental work has provided on this subject, but these difficulties are not discussed and Jackson's hypothesis finds no mention. It seems, to adapt Jackson's aphorism, that our knowledge has achieved a high degree of differentiation but yet awaits integration.

In the light of Jackson's hypothesis, it is submitted, this integration has long been possible. Perhaps the pith of his contribution is his realization that the notion of the localization of a single unit of movement in a single cortical point is not in accord with the facts of clinical and experimental observation, and that there is more, physiologically con-

sidered, than a single movement in a single point. This conclusion is indeed implicit in the facts of observation, but appears to have escaped notice by all but Jackson.

Once it is accepted, however, the difficulties and inadequacy of the punctate localization theory vanish, and the phenomena of facilitation and deviation assume a greater significance as necessary and integral factors in an ordered plan of representation. For, on Jackson's hypothesis, we see that the variations in motor response of a given cortical point—on electrical stimulation—from moment to moment no longer require us to suppose that localizations change in space in the improbable manner hitherto assumed, but are fully accounted for by changes in the relative thresholds of excitability of the different patterns of excitation (different representations) localized in a given cortical point, under the influence of facilitation.

(iii) *Clinical and Experimental Hypotheses Synthesized*

We may now return to Jackson's hypothesis in the attempt to correlate it with the facts of experimental observation. The view that, for example, thumb-index movements are widely represented throughout the motor cortex, but maximally represented at a focus within their wide field of representation implies that at this focus thumb-index movements are more abundantly represented than are other movements : the mediation of thumb-index movements is the principal function of this focus. That is to say, that at this point there is a grading of localizations, and that thumb-index movements have the lowest threshold of excitability—or that theirs is the predominant pattern of excitation—and they appear, therefore, as the primary movements on brief electrical stimulation. Nevertheless, the fact that even in these circumstances, secondary, tertiary and even quaternary movements may follow the primary movements in sequence, strongly suggests the presence at that point of multiple representations of varying thresholds. There is other evidence to this effect. As long ago as 1883, Unverricht (cited by Schafer, 1900) noted that the isolation of a cortical point by cutting round it did not prevent the

spread of an epileptiform convulsion evoked by electrical stimulation of that point, and also that division of the corpus callosum did not prevent this spread from involving the muscles of the opposite half of the body. The second of these observations is in accord with Jackson's earlier expressed view that "discharge" from a single motor cortex may evoke bilateral convulsions, while the first observation has been recently rediscovered by Dusser de Barenne and Marshall (1931) and adds significant support to Jackson's hypothesis. By the latter observers, a cortical point was isolated from the surrounding motor cortex by the injection all round it of novocaine. Prior to this injection the point yielded isolated finger flexion. Subsequent to it, the point yielded not only augmented flexion but also a spread of motor responses to other joints of the same limb and even to other limbs. This finding seems to indicate that facilitation —induced, as they suppose, by isolation—allowed stimulation to reveal the point's whole repertoire of motor representations.

We must conclude, therefore, that, as Horsley has emphasized (1909) all that a brief threshold electrical stimulation of a cortical point does is to sample the point, and not to reveal its full physiological possibilities, and we must abandon the assumption that this sampling can be made the direct and unqualified basis of a theory of the mode of cortical representation of movements.

Jackson's hypothesis is that what the motor cortex represents are the normal movements of the individual, as we see them under normal conditions. In the case of what he calls the leading parts, *e.g.*, the hand, with their great repertoire of complex movements and the widespread subordinate movements normally and necessarily associated with them as, in his phraseology, automatic components, extensive fields of cortex are involved, and these fields overlap and are, as it were, interwoven or interrelated. Within such a field there is a focus in which hand movements are more numerously localized than other movements, the patterns of excitation laid down by the long process of the learning of purposive movements are here mainly those concerned with hand movements. The function of this focus is predominantly, but not exclusively, to initiate hand

movements, and these are the primary movements revealed by the "sampling" of the electrical stimulus, and the movements first activated in normal conditions of cortical activity.

But since parts of other patterns of excitation are also present here, we get as secondary and tertiary responses to electrical stimulation, movements of other parts, those normally associated with hand movements.

As we pass from this focus we reach regions of cortex in which the foci of movements of other leading parts are situated. That is, at any given point in the motor cortex the neurones form the substrata of numerous patterns of excitation, but one pattern predominates and is the first to be "fired off" by appropriate stimulation. If now, by appropriate antecedent local stimulation, the focus of thumb-index movements is facilitated (by lowering of their threshold of excitability), a corresponding depression of excitability of the other patterns of excitation there must ensue, and the area over which thumb-index movements will be evoked will increase in extent. Thumb-index movements will now appear as primary movements in points from which prior to facilitation other movements were evoked as primary movements. Yet what has happened is not, as the punctate theory supposes, that the relation between cortical focus and peripheral muscles has been "broken down," but that the relative threshold values of the different patterns have changed. In short, the localization (representation) of movements in the cortex does not change spatially, there is merely a change in excitability and this necessarily leads to deviation of response.[1]

While aware of the false air of clarity that a graphic

[1] In this connection it is interesting to study Penfield and Boldrey's (1937) Fig. 25, which reveals that all the movements evoked by them were obtainable over far wider fields than are allotted to them in the usual cortical charts of movement. In fact, all the fields allotted to "parts" overlap widely. On the other hand, their "homunculus" portrays a state of affairs that we must find it difficult to accept as representing anything obtaining in the cortex, for while the thumb has a very extensive representation, the representation of the index is very small—being equal to that of the little finger only. The wrist also has a very small representation. Yet, as we have seen, these three parts are almost invariably in action together, and it is difficult to accept so gross a discrepancy between the functional importance of the thumb and that of the index as this figure proposes. Leyton and Sherrington did not find it so in anthropoids.

expression may lend to obscure or erroneous notions, we may risk an attempt to portray these considerations in a diagram, which seeks to correlate Jackson's conception of the cortical representation of movements with the phenomena of facilitation and deviation of response (Fig. 16).

If we accept this scheme as adequately expressing the *action of facilitation, acting on the background of the plan* of localization of movements postulated by Jackson, it follows that *deviation of response is, not a phenomenon in the same category as facilitation, i.e., a fundamental neural process, but simply one of three possible consequences of facilitation,* the other two being augmentation and reversal of response (the latter being a variant of deviation).

It therefore remains to consider what rôle facilitation plays in the co-ordination of movements, and this requires that we shall discuss yet another aspect of Jackson's hypothesis, one not yet referred to, namely, his differentiation of co-ordination into two elements—spatial and temporal. There are reasons for suggesting that these should be *thought of* separately, even though *in fact* they are inseparable. The plan of representation already considered provides the anatomical substratum of co-ordination in space. Co-ordination in time deals with what he calls the "order of action" of movements : that is, the sequence of movements seen when such a motile part as the upper limb is in action. We have already discussed this order when we described the act of lifting a heavy object. It is relatively fixed, the leading parts, that is, those having the greatest number of different movements at the greatest number of times, coming into action first, followed by more automatic movements of proximal parts in the inverse order of their automaticity. The hand and digits are the leading parts in this instance. Thus, representation of movements may be said to have anatomical and physiological aspects : the cortical field and the order of action respectively. It seems reasonable to infer that facilitation, in virtue of its rôle in effecting augmentation, deviation and reversal of motor response, is a primary factor in determining this order of action—in determining co-ordination in time. Under normal conditions of activity the excitable motor cortex is activated by

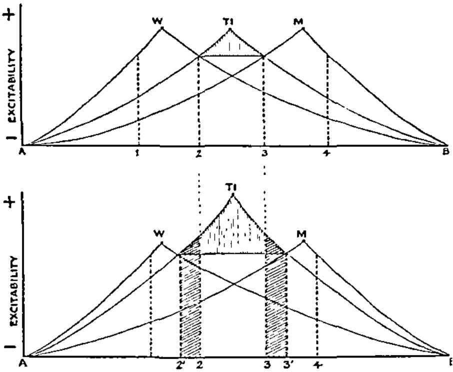

Fig. 16

The base line represents the surface of the motor cortex from midline (A) to fissure of Sylvius (B). The figure A, TI, B embraces the *total* field of representation of thumb-index movements, with its focus from which thumb-index movements are obtained on stimulation as primary movements at, and immediately surrounding (vertical shading) TI. As this total field is followed to its extremes at A and B, the representation of thumb-index movements becomes progressively less the dominant representation in the cortex. A, W, B and A, M, B represent the corresponding fields, with their foci, of wrist and angle-of-mouth movements respectively.

From 1 to 2, along the base line (cortical surface) we have the so-called "wrist area," from 2 to 3 the "thumb-index area" and from 3 to 4 the "angle-of-mouth area." The vertical interrupted lines mark the limits of these "areas."

Excitability is represented by the ordinates.

Fig. X represents a resting state of cortical activity, while Fig. Y represents the state of affairs after thumb-index movements have been "facilitated" by antecedent stimulation of the "thumb-index area." In these circumstances, the total representation of thumb-index and of the other movements remains unchanged, but facilitation has enlarged the cortical area from which thumb-index movements are now elicited as primary on threshold stimulation, making this encroach upon the adjacent wrist and angle of mouth "areas." The cortical region from 2' to 2 now yields thumb-index movements and forms a zone in which there has been deviation of response, and the same applies to the zone 3 3'.

In other words, the initial "thumb-index area" is now surrounded by what we may call an inhibitory fringe for wrist and angle-of-mouth movements.

Yet the total fields of representation have not changed, all that has changed has been the threshold of excitability for these three groups of movements.

higher level (Jackson's highest level) mechanisms in the frontal lobe, and facilitation is probably a process of fundamental importance in this activation. That co-ordination in time is not merely an abstraction having no physiological referent, we may see, as Jackson pointed out, in the behaviour of the convulsion beginning unilaterally. In this we have, not a normal sequence of movements, but a simultaneous "contention," a "clotted mass" of movements *that should follow in sequence. Thus a convulsion* may be rightly spoken of as a disorder of co-ordination in time.

One other aspect of the punctate localization theory may now be discussed, namely, the notion that co-ordination *in space, the building up of a movement-complex, normally* occurs by a simple summation of units of movement. If we accept Jackson's view that each normal acquired movement pattern has its own special representation, it seems unnecessary to suppose that this building up from elementary units occurs on every possible performance of such a movement, though in the formation of new movements some such process may occur. As already pointed out, we have no conclusive proof that the items of movement evoked by brief liminal electrical stimuli are true physiological units of function, and therefore no clear grounds for supposing that the excitable motor cortex is no more than a vast storehouse—or keyboard, to vary the analogy—of hypothetical units of movement.

If, indeed, all that happens when we carry out some complex skilled movement of the hand is that this is built up *ad hoc* from unit components, in what does the *learning* of such a movement really consist? It must involve the laying down in the motor cortex of some permanent trace, or some more or less persisting modification of the physiological substrata of movements, and this is merely another way of saying that the movement is, in fact, represented in the cortex in its natural and complete form.

It seems probable, therefore, that, as Jackson supposed, such a group of highly complex movements as those engaged in articulate speech are, in fact, represented as such in the motor cortex. Theoretically, the matter may be looked at

in either of two ways: If the cortex represents only elementary units of movement, then a normal purposive movement complex results from a "making up" of units. If, on the other hand, we suppose such movement-complexes to be laid down as such in the cortex, then the item of movement we evoke by a brief electrical stimulus results from a "breaking up" of this representation. There is something to be said for regarding the latter sequence as the more consonant with cortical function. This involves a brief reference to Jackson's well-known theory of evolution of function in the nervous system, and some consideration of what is implied in the term "integration."

Jackson's three functional levels suppose a re-arrangement of the nervous control of movement on each succeeding level. On the lowest level we have a "centre" in which lie the anatomical and physiological substrata of a few movements of a restricted part. On the middle level (which he identifies with the motor cortex), a unit of function contains the substrata of a more complex series of movements of a wider field of musculature, while in the highest level each unit is concerned with a group of highly specialized movements of a still larger muscular field. Further, as we rise from level to level, we find not only the greater differentiation of function outlined, but a corresponding increase in interrelationship between the units of the level. In other words, integration keeps pace with differentiation. It is not here possible to discuss in detail the clinical facts of observation that support this notion, for this the reader must be referred to Jackson's papers on the evolution and dissolution of function in the nervous system. Perhaps the simplest way of exemplifying the differences between, let us say, the middle and highest levels, is to consider the results of destroying lesions. Hemiplegia is the characteristic expression of middle level "paralysis," while aphasia, the loss of a highly complex category of movements with the preservation of the action of the muscles involved when simpler movements are in question, is one expression of a highest level "paralysis." Possibly, the immobility and lack of motor initiative of some cases of frontal lobe lesion may express another form of paralysis on the highest level.

Here we have a diminution of activity of the entire musculature for the most highly complex actions.

It is not in harmony with such a plan of physiological organization now to suppose that what is localized in a functional unit of the motor cortex is no more than a minute item of movement, involving a minimal field of muscles. This would be to reduce the cortex to the level of a spinal reflex centre and to deny it integrative function.

Turning now to the effect of destroying lesions, in so far as these throw light upon the plan of cortical motor representation, we find that both in man and in experimental animals there is a considerable and rapid restoration of motor function after local cortical lesions, but that this restoration is not complete. For example, Bard (1938) finds that hopping and placing reactions are permanently lost after appropriately placed local ablations. In other words, compensation is not absolute. Nevertheless, *on the basis of the punctate localization theory it is virtually impossible to account for any restoration at all.* If, for example, the movements of the chimpanzee's hand are really wholly and exclusively represented in the "area" apportioned to them by physiologists, how can there be any restoration of motor function in this member after excision of this representing part? This restoration is only to be accounted for on such a plan of fields of representation as Jackson has postulated. Ablation of the "hand area" can be no more than the ablation of the focus of hand movement representations, an ablation still leaving intact numerous subordinate representations. These rapidly become called in to substitute for the movements lost, and up to a point they do so. Clinical experience shows clearly that this is precisely the state of affairs in man after local cortical lesions. The finest movements of leading parts are lost, but many simpler movements of these parts remain. In short, the effects of destroying lesions of themselves provide cogent evidence in support of Jackson's view and reveal the inadequacy of the punctate localization theory.

In conclusion, it is difficult to see, on the experimental evidence available to us, what other mode of representation than that proposed by Jackson can obtain in the motor

cortex. Moving parts must, in respect of their numerous and varied movements, have wide representations, and cortical points contain multiple representations. Even the unphysiological stimulus of a brief liminal faradization commonly evokes not only a primary movement, but also secondary and tertiary movements in sequence. In Leyton and Sherrington's list of over 500 recorded movements evoked in this way, we are struck by the frequency with which primary thumb and index movements are followed by secondary wrist movements, and primary wrist by secondary digit movements. These findings surely reveal the presence of multiple representations in a given cortical point, and their possession of different levels of excitability. It is probable that a still lingering tendency to think of a representation of muscles rather than of movements in the cortex is in some measure responsible for the continued acceptance of the punctate localization theory. Jackson himself said that "the distinction between muscles and movements is exceedingly important all over the field of neurology. I think the current doctrine of 'abrupt' localizations would not be so much in favour if it were made" (*loc. cit.*, Vol. I, p. 421).

It is therefore submitted that as in 1870 experimental studies confirmed and amplified the *fact* of a cortical representation of movements as inferred by Jackson from clinical observation, so, later, the experiments of Sherrington and his co-workers have confirmed the validity of his inferences as to the *mode* of the representation. Widely as the methods of approach and the terminologies employed have differed, the facts are capable of harmonious synthesis.

III.—The Characteristics of Convulsions beginning Unilaterally

The many detailed descriptions of the different varieties of Jacksonian fit that are to be found in the writings of Jackson, Gowers (1874), Mercier (1881) and others during the period beginning at about 1870 reflect both the intense clinical and physiological interest these phenomena excited at the time, and the high level of clinical observation that

characterized the neurology of the day, and make its literature so refreshing a contrast to much current clinical writing. Indeed, these pioneer observers left but little new to be said on this subject. In a recent paper Gordon Holmes (1927) has given an interesting general account of Jacksonian fits, and has raised some important points to which subsequent reference will be made.

In this paper we are concerned solely with the variant of Jacksonian fit that arises in the motor cortex, the "convulsion beginning unilaterally" of Jackson's nomenclature, and a summary of its main features may be given. For this purpose it is convenient to employ Mercier's (1881) scheme of the musculature. He divides the muscles into series: one series for each limb, one for the head and neck and one for the trunk. A limb series stretches from the apex of the limb to its base; the highest members being at the free extremity, the lowest at the base of the limb. In the upper limb, for example, the highest members of the series are at once the smallest muscles, and those having the most numerous and most special movements, *i.e.*, the most varied ones. On the other hand, the lowest members of the series at the base of the limb are at once the largest muscles and have the simplest and the smallest range of separate movements. In the head and neck, the muscles of the eyelids and those round the mouth are the highest of the series, those of the neck the lowest. The lowest members of all the series are the muscles most often employed in bilateral movements. We may now consider seriatim the various aspects of the convulsion (*cf.* Mercier, *loc. cit.*).

1. *Focus of Onset.—It is the rule, though not without exceptions, that the fit begins in the highest members of a series.* Thus convulsions, beginning unilaterally, almost always start from one of three foci: thumb and index, angle of mouth, or great toe, in this order of frequency. Rarely, a focal convulsion may start in the lowest members of a series, *e.g.*, in the muscles at the base of a limb, but a convulsion starting at any intermediate situation is of extreme rarity.

2. *The March of the Convulsion.—The convulsion which starts in the highest members of the series, i.e., at the apex of the limb, tends to "march" centripetally to the base of the limb,* that is to

the lowest members of the series. The spread is a *compound spread*, *i.e.*, a spread both in intensity and in extension. It is not a mere passage of convulsion up the limb in which all the muscles become equally involved, or in which convulsion ceases in the highest members of the series as those lower in the series become involved. That is to say, the muscles first convulsed become so more severely as the spasm spreads to those lower in the series. Thus, in the case of the upper limb there is (i) spasm in muscles of thumb and index, (ii) more severe spasm in these muscles and spasm in muscles moving the remaining digits, (iii) more severe spasm in the two groups already named, and spasm in some muscles moving the wrist, (iv) the spasm increases in the muscles already involved and more muscles moving the wrist enter spasm and some moving the elbow. Thus, step by step, the convulsion reaches the lowest members of the series, the muscles moving the shoulder.

The next step, if spread continues, is the entry into convulsion of muscles of other series. Thus, in the case already cited, the muscles of the hand and neck or those of the leg may become involved.

It is the rule, again with exceptions, that when convulsion passes from the first series—in which it has spread centripetally from the apex—to a second or further series, it begins in the lowest members of the new series. Thus in the passage of a convulsion from leg to arm, the muscles moving the shoulder enter into spasm first, spread then occurring *centrifugally* to the apex of the limb. The order of further spread becomes increasingly difficult to detect because it becomes increasingly rapid and tends to convulse the muscles of the series later involved almost simultaneoulsy. The order of spread is as follows : unilateral muscles of side of onset, bilaterally acting muscles (chest and sometimes trunk) of both sides, unilaterally acting muscles of crossed side. In detail, the following is the sequence given by Jackson, in the case of a convulsion beginning in the (i) *arm*, thumb and index fingers and forearm, upper arm ; (ii) *face*, cheek drawn up, eyes deviated, head deviated ; (iii) *leg*, thigh, leg, foot and toes ; (iv) *bilaterally acting muscles*, temporals and masseters (clenching jaw), thoracic and abdominal muscles ; and (v) *unilaterally*

acting muscles of crossed side; the sequence here may be difficult to follow, but arm probably enters into spasm before leg, the spasm is more nearly contemporaneous, of shorter duration and tends to be tonic.

3. *Attitude assumed by Convulsed Parts.*—In virtually all cases the limb series initially involved is flexor, so that an attitude of flexion is taken up, sometimes in the case of the arm with abduction and elevation. Holmes records that forced passive extension of the arm in these circumstances may change the clonic spasm over to the limb extensors, the process involved may—it is suggested—be akin to that described by Magnus under the name of "Schaltung."

4. *The Extent of the Convulsion.*—Spasm may remain restricted to the muscles initially involved, or it may spread to and remain within the limb series. In other cases all degrees of spread until the convulsion becomes generalized are to be met.

5. *The Rapidity of Spread.*—Those convulsions spread farthest that spread most rapidly, and there is also a tendency for fits in which the clonic convulsions have the fastest rhythm to spread farthest and fastest. There is an unbroken series of grades of convulsions from those that remain confined to the focus of onset, have the slowest rhythm and least intensity of convulsive movements, and last longest, to those that spread so far and so rapidly that the convulsion appears to become universal almost at once. Fits of all these grades may be seen in the same individual on different occasions, so that on one occasion he has an unequivocally focal or "Jacksonian" fit, and on another a generalized fit—with loss of consciousness—that can scarcely of itself be distinguished from a fit of "idiopathic epilepsy." In this connection a statement of Mercier's (1881) is of interest. He says (*loc. cit.*): "In fits of deliberate march the spasm may be three or four seconds in spreading from muscles of the highest order to those of the lowest, and seven or eight in becoming universal. In rapid fits, in which the convulsion appears to be universal from the very outset, it may be impossible to determine the point of origin except *inferentially* by observing the part *most* affected.

Fits of deliberate march are usually due to gross disease of brain tissue, and it may even be said with some approach to accuracy that the coarser the structural alteration the more deliberate the march. Thus the convulsion whose outset is slowest of all are those arising from tumours of the brain."

6. *Duration of Fit.*—Those fits that remain restricted to the small group of muscles in which they arise, *e.g.*, thumb and index muscles, tend to last the longest, and such an attack may last for many minutes or even for a considerable fraction of an hour. The faster and the farther a fit spreads, the shorter usually its duration.

7. *The Quality of the Convulsion, i.e.*, whether the spasm is tonic or clonic. It is generally regarded as characteristic of the Jacksonian convulsion that it is clonic, but most observers have recorded the fact that it may be tonic at first, and for a few seconds, then becoming clonic. In general it may be said that the convulsion that remains restricted to a narrow field of musculature and is prolonged tends to be clonic from the outset, but the rapidly spreading convulsion may be tonic for a few moments before the spasm begins to intermit, *i.e.*, to become clonic.[1]

8. *Affection of Consciousness.*—The convulsion that remains restricted to a single series or to the higher members of a series is not attended by any alteration of consciousness. Consciousness is lost in spreading convulsions, and at a stage which varies directly with the rapidity of the spread. Thus in a rapid spread, consciousness may be lost when a convulsion, starting in the hand and subsequently involving head and neck, enters the lowest members of the leg series. In more slowly spreading attacks, consciousness may not be lost until the bilateral muscles of both sides become involved (*e.g.*, trunk muscles). In yet others, consciousness is lost as the crossed limbs enter convulsion.

[1] Penfield and Erickson (1941) state that a convulsion arising in the cortex is clonic, and that a tonic phase is added when the subcortical grey matter becomes involved. Yet this can hardly be the case, either for convulsions beginning unilaterally or for those that are generalized from the start and show an initial loss of consciousness (idiopathic epilepsy). For in the former, tonic spasm not rarely precedes clonic, and in the latter invariably does so, and from these facts we should have to assume—according to these authors—that all such fits arise in subcortical grey matter, the cortex being only secondarily involved.

9. *The Influence of Peripheral Stimuli on the Convulsion beginning Unilaterally.*—One of the most interesting phenomena of the Jacksonian convulsion, and one very early recognized, is the influence of peripheral stimuli applied to the part convulsed. It is less widely recognized that this influence may be in the direction of (*a*) increasing, as well as of (*b*) diminishing or abolishing the convulsion. In one of his early papers (1870, "A Study of Convulsions") Jackson discussed the abolition, or inhibition, of the convulsion by various forms of peripheral stimulus, *e.g.*, a ligature applied to the extremity in which the convulsion was apt to start, or a blister. Other modes of stimulus described are violent rubbing of the part, powerful voluntary contraction of the muscles, etc. This is true not alone of Jacksonian, but also of the generalized fits of the so-called idiopathic epilepsy.

An interesting case is described by Buzzard (cited by Gowers, 1874) in which Jacksonian fits, associated with a tumour of the *left* cerebral hemisphere, began with paræsthesiæ in the region of the *left* wrist (*i.e.*, the homolateral wrist). When a blister was applied to this region the "aura" changed over to the right wrist, until the blister had healed, when it resumed its original situation.

It appears to be a common character of all these inhibiting peripheral stimuli that they are of some duration, that is, they are persistent stimuli.

In contrast to these observations are those in which brief recurrent stimuli, to the part in which focal convulsions arise, precipitate the attacks. Jackson reports instances of the kind (*loc. cit.*, pp. 2 and 7), and recently Gordon Holmes (1927) has stated that "many patients subject to Jacksonian epilepsy commencing in one hand, for instance, are careful to shield this hand from injury or stimulation of any kind, and they frequently attribute a seizure to some irritation or accident to it. . . . I have been able in certain cases to induce typical local spasms in a hand or foot by repeated stimulation of it. The most effective means is usually a long or regular series of tactile contacts with a wisp of cotton wool, or von Frey's hairs. The attack induced usually commences with a few clonic movements, or a curious purposeless restlessness, and may extend no further if the

stimulation is stopped ; sometimes, however, they spread and may involve the whole of one side of the body. These movements start almost invariably in the part that is being tested." Bubnoff and Heidenhain and François-Franck's experiments, already cited, are of relevance here.

We may say that rapidly repeated brief peripheral stimuli to a convulsing part will initiate a convulsion, but will not cut short one already started, and that a persisting cutaneous or deep stimulus to a convulsing part is more apt to stop than to start a convulsion.

In one personally observed case the facilitating and the inhibiting effects of peripheral stimuli were exemplified. At periods when the patient's attacks were arising in the thumb-index, he found that tapping his wrist or his elbow against the edge of the table precipitated an attack, and he also found that an attack once started could often be cut short by firmly grasping the right wrist with his left hand and maintaining the grasp for half a minute or more. Here different orders of stimulus (in the one case recurrent brief stimuli, in the other a single sustained stimulus) to the convulsing part showed reverse effects—facilitation and inhibition.

10. *Other Motor Concomitants of Convulsion : Loss of Power.*—A sudden loss of power in a part is a familiar feature in the range of Jacksonian attacks. It may on occasion be the sole manifestation, it may precede convulsion in a given part, or it may precede convulsion in another muscle series. In yet other cases, loss of power may characterize some fits, convulsion others. Holmes (*loc. cit.*) reports such a case.

11. *Sensory Concomitants of Convulsion.*—In a considerable number of cases of convulsion beginning unilaterally, there are no subjective or objective sensory concomitants in the convulsed or in other parts, but in not a few cases of the kind subjective sensory phenomena may precede or accompany spasm or loss of power. These may appear in the part weakened or convulsed, or in some other part. Thus Jackson records the development of sensations of numbness in the hand to be followed immediately by clonic spasm in the face. This numbness may accompany weakness of the part affected, or occur without this.

In the case already cited numbness and weakness of the right hand may precede by a very few seconds the onset of spasm in the face, and examination of the hand at this time—made on several occasions by the writer—revealed not only impairment of purposive movements of hand and digits, but also sensory impairment of cortical type (defective localization of light touches, markedly raised threshold for compasses, impaired sense of position and error of projection in finger—finger test with eyes covered). These defects, *i.e.*, loss of power and of sensation, persisted for from two to four minutes after the cessation of the longer attacks (which endured for as long as five minutes under observation). Appreciation of the pain of pin prick was not impaired.

In another case, one of Jacksonian convulsions beginning in the left great toe and spreading up the leg, and sometimes to the arm, the patient was subject to attacks of three grades of severity.

(i) The mildest attacks consisted of a feeling of numbness in the foot up to the knee, together with paresis of the limb, but no spasm. (ii) More severe attacks consisting of stiffness of the leg which after a few seconds drew up clonically, numbness accompanied these phenomena. (iii) The most severe attacks consisted of an onset of rigidity with inversion of the foot and *flexion of the toes. Then the leg jerked spasmodically and* powerfully. The left arm was usually unaffected, but on some occasions it went " limp " and she dropped whatever she might be holding in it. During and for a time after the attack the leg felt numb and " like a piece of strange warm flesh," this sensation —together with paresis—lasting for as long as half an hour.

In all these attacks, therefore, even in those in which no convulsion occurred, subjective numbness of the affected part was present.

12. *Residual Paresis of Convulsed Parts.*—That the muscles engaged in a Jacksonian convulsion subsequently show a transient paralysis was originally recorded by Todd, a phenomenon accounted for by Jackson in the statement, " Parts of the central nervous system are temporarily exhausted by epileptic (that is, excessive) nervous discharges," and exhaustion has since been generally accepted as the explanation of this phenomenon. Jackson further pointed out that in character and in incidence, this paralysis has all the characters of that resulting from a destroying

lesion of the "middle level," that is, the parts having the most numerous and most special movements at the greatest number of different times, *i.e.*, the most varied uses, are those most severely affected, while the parts having the fewest special movements, *i.e.*, the least varied uses, either escape or are relatively lightly affected, according to the severity and extent of the destroying lesion. Thus he speaks of a Jacksonian convulsion involving the musculature of one side as "the mobile counterpart of hemiplegia." The implications of this view will be considered in a later chapter.

The preceding summary embodies the main features of the "convulsion beginning unilaterally," the Jacksonian convulsion, and we may now proceed to view them in the light of Jackson's hypothesis of cortical representation, and that of the experimental observations and inferences already described.

IV.—The Cortical Representation of Movements as Exemplified by Jacksonian Convulsions

The inference runs through all writing on this subject that the "march" of a convulsion expresses a spread of excitation through the cortex from point to point, each point successively excited discharging the movement represented therein. Jackson explicitly repudiated any such view, though he admitted that spread of excitation did occur in the more widely extending convulsions. The inference that a focal fit, becoming general in the musculature of the half of the body in which it began, involves a total discharge of one motor cortex is not one the facts allow us to make. The experiments of Unverricht and of Dusser de Barenne and Marshall, already cited, make it clear that spread of *convulsion* can occur even though the discharge may remain restricted to the original cortical focus—which discharges successively its content of motor representations according to their threshold of excitability. Further, a fit beginning in one hand and then spreading to arm, leg, face and chest muscles so as to produce a "mobile counterpart of hemiplegia" has not the same pattern as a similarly spreading fit beginning in the hallux. The total composition of the

discharge may be the same in the two cases, but its pattern or constitution is not the same. We are not dealing, therefore, with two total and identical discharges.

We may conclude, therefore, that a spreading *convulsion* does not necessarily imply a directly proportional spreading cortical *excitation*. The field of convulsion (in the musculature) is probably always much wider than the field of excitation (in the motor cortex).

A Jacksonian fit that remains throughout restricted to, let us say, muscles moving thumb and index is a relatively leisurely clonus of moderate intensity and often considerable duration. It has neither the rapidity of rhythm nor the intensity of convulsion that occurs in these muscles when the convulsion spreads up the limb, *i.e.*, it is probably not a total discharge of all movements represented in the cortical focus of origin.

Therefore, the compound order of spread (increase in intensity as well as spread in incidence) is not readily explicable on the old punctate representation theory, but is explicable on Jackson's hypothesis of representation.

There is yet another feature of the Jacksonian convulsion not explicable on the punctate localization theory, namely, the fact that virtually every such convulsion starts from one of three foci—thumb and index, angle of mouth, great toe. There is nothing in the old theory that renders this feature explicable, yet on Jackson's hypothesis it is comprehensible. It is a reasonable inference from all that has been advanced, that the named topographical motor " areas " of the familiar cortical map of the physiologist represent no more than the foci of the main localization of the movements of the parts in question and not their total field of representation. In virtue of their vast range of movements, Jackson's " leading parts " have wide fields of representation. In other words, the movements of these leading parts have the most extensive cortical foci of minimal threshold of excitability of all movements represented in the cortex. *It is suggested, therefore, that Jacksonian fits have their three characteristic foci of onset because the movements concerned are those that have the widest fields of low threshold excitability.*

There is a general assumption that when a local cortical

lesion provokes a convulsion, the focus of onset of the convulsion indicates that the lesion in question necessarily lies within, or contingruous with, the cortical "area" corresponding to the movements involved. Yet even cursory consideration of the pathological facts forbids us to entertain a notion so naïve. There are few known lesions so small and sharply circumscribed as to make a precise and exclusive localization of this order possible—even the smallest astrocytoma is always much larger than its visible extension, and it is impossible to suppose that pathological lesions in the cortex have some special affinity for the thumb-index, angle of mouth or great toes "areas."

Broadly speaking, it is probably true that a lesion near the vertex is likely to fire off a Jacksonian fit beginning in the great toe, and one near the foot of the precentral convolution will fire off a fit beginning at the angle of the mouth, but, nevertheless, nothing so fortuitous as the *precise* site and limits of the lesion within the motor region can account for the prevalence of the three foci of onset so typical of Jacksonian fits. We must, therefore, turn to some quality inherent in the mode of cortical representation for an explanation of the plain facts. This quality is the mode of representation embodied in Jackson's hypothesis.[1]

A minor feature of Jacksonian fits remains to be mentioned, namely, that *the order of spread is not invariably that indicated on the familiar topographical charts of the motor cortex.* Thus, spread from upper limb to face should be, on this basis—as Jackson surmized—from shoulder to orbicularis, but more commonly it is from shoulder to angle of mouth. Sometimes, also, the spread is from foot, through leg and thigh, to hand and not to shoulder, though the latter sequence is the more common. Yet another sequence occurs

[1] A characteristic of the fits produced by the cortical venous angioma, in the writer's experience, is that the focus of onset of the Jacksonian fit varies from time to time in the same patient, beginning most commonly in the hand, but sometimes in orbicularis palpebrarum and sometimes in angle of mouth or in tongue. Again, for considerable periods, one focus of onset prevails, giving place then for a subsequent period of time to another focus of onset. This variable feature, together with the recurrent development of fits which generalize so rapidly with loss of consciousness that the focus of onset cannot be detected, is submitted as a differential diagnostic feature of value in the case of cortical venous angioma. In the case of tumour, the focus of onset tends to remain almost or quite constant.

in a recently observed case: thus, foot, leg, muscles of abdominal wall, angle of mouth, orbicularis palpebrarum, head and eyes (deviation), hand, arm, shoulder—loss of consciousness and general bilateral convulsion followed by transient residual hemiparesis (left-sided).

On the whole, attacks beginning in, and restricted to the face, appear to start in orbicularis palpebrarum, and thence by side of cheek to angle of mouth, tongue, jaw and neck (deviation of head): that is, from highest to lowest muscles of the head series. Yet this focus of onset is not the invariable one. In so far as they have significance, these deviations from the pattern of the cortical chart of movements associated with the punctate localization theory are less difficult to account for on Jackson's hypothesis.

Further, there is another feature of Jackson's hypothesis of cortical representation of movements to which no reference has yet been made, namely, that movements of both halves of the body are represented in the motor cortex of each hemisphere, but that—in respect of a single hemisphere—the representation of the movements of the two sides is not identical—and for the homolateral side is not so rich or varied. Thus, for him, a focal convulsion becoming universalized, yet remains a discharge from a single motor cortex. Unverricht's experiment in this regard has already been cited, yet if a "discharging" lesion can produce bilateral convulsion, it follows that a destroying lesion in one hemisphere should produce *more than hemiplegia*: it should produce loss of movements on both sides, though possibly less severe on the homolateral side (*i.e.*, side of lesion). Readers familiar with Gowers' textbook (1893) will recall the author's account of the impairment of movements and the increase of tendon reflexes invariably to be found on the side of the lesion in very or moderately severe cases of hemiplegia. It is not exceptional for a transient ankle clonus to be evocable from the side of the lesion, but —as indicative of the different quality of the cortical representation of the two sides of one hemisphere—a homolateral extensor response, or a homolateral loss of abdominal reflex is not part of this bilateral affection that we call hemiplegia.

Indeed, the clinician who has closely studied hemiplegia

in all its stages and grades of severity cannot escape the conclusion that there is some measure of impairment of movements—in cases of any severity—on the side of the lesion. This is perhaps more evident in trunk than in limb muscles, a fact that would accord with Jackson's view that these are the movements possessing the greatest measure of bilateral representation.

Hemiplegia commonly arises not from a destroying lesion of the cortical representation of movements, but from one involving the efferent projection path—the pyramidal system—from this cortical region. Convulsion arises from lesions in grey matter, hemiplegia from those in white. The pyramidal system is now known to contain approximately a million fibres, and their functional pattern must stand in close relation to that of the cortical cells in which they arise. Just as the movements of the leading parts require for the representation of their movements a predominant part of the motor cortex, so also they call for a proportionate quota of the efferent pathway therefrom. Hence a partial destroying lesion of this pathway will produce the same pattern of movement disorder, loss of function in this case, that a stimulating lesion of the motor cortex produces. Thus, in hemiplegia we have a special incidence of loss in the movements of the leading parts.

We may conclude, therefore, that just as the behaviour of a Jacksonian convulsion is not compatible with the classic punctate (and unstable) localization theory, so also the negative phenomena of hemiplegia are not less irreconcilable with this theory and require such a mode of representation as Jackson postulated.

It may be added that physiological literature contains many references to epileptiform convulsions of Jacksonian type evoked by strong or prolonged electrical stimulation of the cortex, and within recent years a most ingenious technical method has been devised (Fender, 1937) to produce these convulsions at will, yet none of these descriptions approach in detail or precision the accounts current in clinical literature, no attempt has been made to draw inferences as to the mode of cortical representation from them, and hence they add nothing to what we may glean from clinical sources.

Loss of Movements during and subsequent to Jacksonian Attacks.—We have seen that sudden and transitory loss of movement may be the sole expression of a focal attack, or may precede spasm in the affected or in other muscles in an immediately following convulsion. Jackson records several such cases, and Holmes has recently recorded one in which some attacks, loss of power, and on others, convulsion in hand and fingers occurred.

In this connection the transient loss of speech that may precede a Jacksonian fit developing in the right face must be regarded as in the category of loss of power. It is generally believed that this is the only mode of speech disorder in Jacksonian fits, but two personally observed cases made it seem reasonable to assume that we may get convulsion in the muscles of articulation producing a vocalization. In one case the following sequence was recorded :—

> The fit begins by a sudden loss of power in the right hand, so that he drops what he may be holding. In a second or two, during which time the hand and wrist go numb, and then pass into a clonic convulsion spreading up the arm to the shoulder, he finds he cannot speak and his tongue seems to curl up against the roof of his mouth. He then utters a sequence of distinct "D" sounds (d-d-d-d-d-d), and as this happens the mouth begins to be drawn to the right and to quiver.

A similar phenomenon of apparent articulatory spasm was noted on some occasions by another patient.

It seems, then, that movements (those of the limb as well as those of the muscles of articulate speech) may be suddenly paralysed, or suddenly put into spasm, or first paralysed and then convulsed.

There seems no escape from the conclusion that in these two distinct effects we are dealing with "discharge" from different cortical foci, from foci which inhibit movement in the first place, and from those that excite movement in the second ; and if we take this view the observation of Hines (*loc. cit.*) and of Dusser de Barenne, Garol and McCulloch (*loc. cit.*) may have some relevance, and it may be suggested that the phenomena of inhibition of movement in Jacksonian fits afford some measure of confirmation to the notion that there are cortical regions, immediately anterior to the

excitable motor cortex, that normally inhibit movement. Amongst the movements thus differently treated it seems that we may include those of articulate speech.

It has been generally believed that the transitory paralysis of convulsed parts that ensues after convulsion is due to exhaustion of the discharging foci, and in the stage of flaccid coma that ensued upon a major epileptic fit with generalized convulsion Jackson sees the effects of a widespread exhaustion of the highest level representation of movements in the cortex producing universal paralysis. To the objection that the comatose patient does not move because he is unconscious, Jackson returns the following conclusive answer: "I submit that it is not an intelligible explanation to say that the patient does not move because he is unconscious. Why should he not move if unconsciousness were all, his nervous system being sound? The fact is, he cannot be unconscious without having some negative physical condition of his nervous system answering to that negative psychical condition, and it is the central negative physical condition alone which we have to take account of in our explanation of his other physical condition of immobility" (*loc. cit.*, p. 322). In short, the patient is unconscious for the same reason that he cannot move.

Nevertheless, this irrefutable aphorism does not necessarily bind us to "exhaustion" of the highest centres as the valid explanation, and leaves it an open question whether here also, after generalized or focal convulsion, the loss of power that endures for seconds or minutes may not be due to the activity of inhibitory cortical regions, or to "extinction" in other cortical regions normally excitable.

V.—Conclusions

The so-called "classic" theory of the cortical representation of movements proposes a cortical mosaic of "points" in the excitable motor cortex, each of which represents a single small movement, sometimes one activating but two muscles reciprocally. Leyton and Sherrington suggested that it is the function of the motor cortex as a whole to synthesize these fractional components into those

combinations and sequences of larger movements that characteristically make up the normal motor activities of the organism. They also pointed out that a given cortical *point responds to stimulation in various ways, determined* by the stimulation factors to which it is exposed. Thus a point that at one moment yields no response may be responsive at another. Repeated threshold stimuli have two effects—they augment the responses from the point stimulated and may alter ("deviate") the response from adjacent points; even reversal of response may be obtained. This implies an instability of localization, a breaking down, as Dusser de Barenne puts it, of the relations between cortex and musculature. There is yet another assumption in the theory, namely, that the item of movement revealed by a brief threshold stimulation of the cortex is a normal unit of co-ordinated movement.

It is submitted that this theory does not adequately generalize the facts of clinical or experimental observation. These indicate that it is the normal movement combinations and sequences of normal activity that are represented, and this not on the plan of a mosaic of contiguous "localizations," but on a plan of wide and overlapping fields, each of which has a focus wherein the movements of a given motile part are mainly, but not exclusively, localized. The variations in response of a given cortical point to stimulation are not due to any breaking down of the localization, but to variations in the threshold of excitability of the different movements "localized" at this point. Facilitation is the process underlying this variation, and deviation of response is a consequence of this facilitation.

The phenomena of Jacksonian convulsions and of hemiplegia also afford support to the hypothesis of widespread fields of localization that Jackson formulated, and are inexplicable on the basis of the punctate theory of localization.

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On the Notion of the "Discrete Movement" in Willed Motion

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Chapter IV

On the Notion of the "Discrete Movement" in Willed Motion

"*The first cause of absurd conclusions I ascribe to the want of method; in that they begin not their ratiocination from definitions.*"—Thomas Hobbes (1588-1679), *Leviathan.*

It is, perhaps, those scientific notions that we take most readily for granted, and receive upon authority with the greatest assurance, that are most apt to repay examination from time to time, and that upon occasion are found wanting when brought to the touchstone of correspondence with facts. The more abstract such a notion the greater the probability that this will be so. Further, in continued currency, abstract ideas seem to harden so easily into concrete facts, and mental constructs come to pass muster for natural phenomena.

It is primarily to discuss a term and to assess the significance of an hypothesis that has become attached to it that this note is written, and as part of a clearing of the ground for a later consideration of the rôle of the pyramidal system in voluntary movement, to appear in a subsequent paper.

In the physiological literature upon the cerebral motor cortex we may note the increasing use of the term "discrete movement." As far as I can ascertain, this made its original appearance in the classic paper of Leyton and Sherrington (1917) on the excitable cortex of the chimpanzee, orang-utan and gorilla, where it was used as descriptive of those fragmentary movements, *e.g.*, of a digit, or of a segment of a digit, that are evoked upon the application of a punctate faradic stimulus of threshold value and of minimal duration to the excitable cortex of the anæsthetized animal.

The character and the possible significance of the movements so named were clearly expounded by these authors, and no examination of the expression would be called for were it not for the fact that it has recently come to be applied,

without any further definition, to a phenomenon of a widely different physiological order, namely, to a particular category of voluntary movements (Tower, 1940, 1944). The expression has therefore now come to have two distinct objects of reference, and the difference between these two is more profound if we hold with Foerster (1931), Fulton (1946) and Hines (1944) that what characteristically emerges from appropriate electrical stimulation of the cortex is a twitch of a single muscle or of a part of a single muscle, and not a movement in the sense that this implies some element of simple co-ordination (*e.g.*, reciprocal innervation), than if we hold with Leyton and Sherrington (1917) that what are evoked in this way are highly co-ordinated local items of movement.

A confused and equivocal terminology is the fruitful parent of confused and equivocal thinking, and it is necessary to decide whether in a scientific nomenclature we can rightly use the expression "discrete movement" in this loose dual fashion, to ask in what degree the qualifying word is applicable to either category so named, and in particular to consider whether throughout the range of voluntary motor activity as we see it in the normal human subject any specific mode of movement occurs that can accurately be spoken of as "discrete." In other words, is there a physiological process corresponding to the idea embodied in this expression, or is the discrete movement an abstraction, a mental construct, and not a natural phenomenon?

These questions gain their importance in view of Tower's (1940) hypothesis that it is a "unique" and specific function of the pyramidal system to mediate the "discrete" movement, and that movements not of this category result from the activity of extrapyramidal motor systems. It will be seen, therefore, that we have here a clear-cut physiological and anatomical distinction between discrete movements and those deemed not discrete.

At this juncture, clearly, some attempt at definition of the terms "discrete" and "movement" is called for. "*Discrete,*" *the O.E.D. tells us, means* "*separate,*" "distinct," "discontinuous" and "not coalescent or confluent." It will be noted that no dimensional qualification

figures in any of these defining terms, and discreteness is nowhere expressly correlated with amplitude or size. Possibly, it may be thought that "discontinuous and not confluent" most precisely conveys what we have in mind in the general use of the term "discrete," and clearly something that is confluent cannot be discrete. "Movement" might surely seem a term not calling for elucidation. In its general non-technical sense any qualification it may require is supplied by the context in which it is found, but in physiology this looseness of usage is not allowed, and the word has come to connote, not merely a change in the spatial relations of some part, but also, as underlying such a change, a process embodying some element of neuromuscular integration, of which, perhaps, reciprocal innervation is the most fundamental and constant expression.

Tedious as these preliminary considerations may seem, they are essential if we are to avoid, or at least to minimize, that misuse or equivocal use of terms, so much more common in the biological than in the physical sciences, which in the past has led to so much confusion of thought and to such long delays in the logical evolution of ordered knowledge. In the present connection, for example, if it were to be found that the "discrete" movement is merely an abstraction not corresponding to any observed phenomenon, or the term so equivocal that no correlation between it and any observed phenomenon could be established, then we should have to abandon the notion that it is a specific function of the pyramidal tract to innervate discrete movements, for it would have no meaning.

The Response to Electrical Stimulation of the Motor Cortex considered as a "Discrete Movement"

The fragmentary movements referred to by Leyton and Sherrington (*loc. cit.*) as being "discrete" are elsewhere in their paper characterized as "fractional," "separable," "partial," "relatively small," as "local items of movement" and as "in themselves perfect movements": from all of which we may conclude that we are concerned with movements involving notably small fields of musculature and

occurring in the otherwise inert musculature of an anæsthetized animal. Yet in such a case only precise electromyography could tell us how extensive is the field of muscular involvement, and this perhaps only when the musculature as a whole shows a background of tonic activity against which inhibition can be as readily discerned as excitation. Such studies have been attempted, for example, by Cooper and Denny Brown (1927) and, more recently, by Bosma and Gellhorn (1946), though not precisely with this particular end in view. They afford no confirmation of the view that simple muscle twitches are in question, but, on the contrary, they confirm the complex nature of the motor response and its status as a movement, as originally recorded by Sherrington (1906). We may, therefore, define the "discrete movement" occurring in response to the electrical stimulation of the motor cortex as *a process employing a small field of musculature and producing a simple phasic movement of a small movable part against the background of a phasically inert musculature in an anæsthetized animal.* It will be noted that in this physiologist's usage a dimensional qualification of the discrete movement has crept in, and this movement has become small as well as separate.

Before leaving the subject a further reference to the hypothesis that the response to cortical stimulation is a simple twitch is necessary. By means of modern methods of stimulation, for example, the thyraton, the condenser discharge and the sine wave current—the details of which it is not here necessary to discuss—it has been claimed to be possible to obtain finer fractions of movement than were yielded by the simple faradic inductorium used by Sherrington and earlier workers. The twitch hypothesis of the nature of the cortical motor response derives mainly from studies made by these methods. Thus, Wyss and Obrador (1937), working in Fulton's laboratory with condenser discharges, obtained what they describe as a "short twitch," and what Fulton (1946) speaks of as "beautifully discrete responses." But their analysis of the muscular response consisted only in simple inspection and palpation, and in a footnote in their paper they state that "the term 'twitch' is used to describe a brief contraction

which may or may not be a twitch in the technical sense." Thus the matter is carried no further, for both method and terminology lack the necessary scientific precision.

Hines also (1944) discusses this question at length, but without any clear conclusions, and makes the following significant statement that " the results of electrical stimulation of the precentral cortex do not demonstrate the ability of that region to produce movement *per se*; rather, they illustrate what the neuromuscular mechanism can do when a current of particular form and intensity is applied to the cortical surface." Here, in this flash of insight and candour, we find bluntly stated the narrow limitations of this experimental method, which, while it does reveal the excitability and the motor function of the precentral cortex, does not tell us anything very clearly of its physiological organization.

Nevertheless, even if adequate electromyographic studies do ultimately reveal that simple muscle twitches can result from electrical stimulation of the cortex, we are still left with a muscular response which may be called discrete in that it consists in a simple phasic contraction of a small field of musculature *against the background of an inert musculature.*

A point of some theoretical interest arises here, for the view that both muscular twitches and movements can arise from cortical action opens up a long vista of discussion about the whole problem of the physiological status of the motor cortex in the co-ordination of movement. It involves the conception of the pyramidal system; the final product of the evolution of the motor system in the brain, as having a simple function of direct innervation of individual muscles; a function not essentially different from that of the ventral horn cell of the spinal cord. It is hard to see how such a notion can be compatible with any view of the central nervous system as an integrated and integrating system, and it must surely involve the abandonment of much that is still generally accepted as firmly established and as fundamental in the teachings of Hughlings Jackson and of Sherrington. The relevant literature shows no sign of recognition that these implications are inherent in the

proposal that the motor cortex innervates muscles and not movements.

Finally, before passing to consider the voluntary movement as showing a specific "discrete" component, some reference should be made to the profound difference between the motor response to electrical stimulation of the motor cortex and the voluntary movement. The method of punctate electrical stimulation is as artificial and unphysiological a mode of activating the cortex as could be imagined, and to assume that we may directly compare the motor response evoked by this means with a voluntarily *induced movement is without warrant. If, despite the* dangers thereof, we have recourse to metaphor, the evoking of movement by faradizing a point on the surface of the cerebrum is a kind of forcing of the mechanism, to be likened to the breaking open of a safe. Now we do not reveal the intricate workings of a combination lock by blowing a hole in the safe door or by levering this off its hinges. Perhaps by its very crudity the metaphor may serve to direct attention to the great disparity between a voluntary movement normally mediated in the intact organism, on the one hand, and the response forced out of the cortex by electrical stimulation on the other. The various and variable factors that go to determine the characters of the latter response under experimental conditions have been discussed by Hines (*loc. cit.*), and also the influences of the different anæsthetics employed upon the normal spontaneous activity of the cerebral cortex. It appears certain that hitherto we have argued from the results of stimulation experiments to the normal functions of the motor cortex with a freedom that has taken too little account of the very abnormal conditions of experiment. Considerable insight and a very difficult task of interpretation and synthesis are demanded successfully to extract from such experiments any valid conception of normal function, and so far the attempt has been very imperfectly successful.

The voluntary movement, to take but a single feature in which it differs from the cortical stimulation response, is initiated and controlled from its start to its consummation by a constant stream of sensory impulses of diverse sources

which reach the cortex. In the mediation of voluntary movements we can hardly think of a motor cortex, in the strict sense, but only, as clinical neurologists have always insisted, of a sensorimotor cortex.

We may conclude, therefore, that even if we agree that the motor response to the electrical stimulation of the cortex is to be called a "discrete movement," this is wholly irrelevant to the quite separate question of whether the voluntary movement is ever "discrete."

The Status of the "Discrete Movement" in Voluntary Motion

As was mentioned earlier, the importance of the question of the discrete voluntary movement arises from the fact that Tower (1940, 1944) has proposed that "the one unique function of the pyramidal tract" is "its minute control of discrete movement." Throughout two very important and factually illuminating papers, Tower repeatedly returns to this theme in various and varied phrases, sometimes speaking of this function as "the organized control of discrete movement," sometimes as "an organization for the discrete control of movement." Conversely, loss of this function is said to eliminate all "fine usage," all "discrete usage," and to leave behind only "a limited number of stereotyped components" of movement. But even the latter are not left unimpaired when pyramidal function is abrogated, for they now show "loss of initiative," a raised threshold, and an absence of precision and aim. In Tower's view these defects result from the loss of a secondary pyramidal function of "modulating" these stereotyped components and of lending them speed and precision. It should be added, in conclusion, that the stereotyped components of voluntary movement are postulated as being extrapyramidally innervated.

It is not proposed in the present note to give any detailed critical study of this hypothesis as a whole, but its validity depends upon the phenomenal reality of a category of discrete movements, and this is the problem now under discussion. It will be apparent that this discussion hangs

stereotyped components, making a confluent action in which discrete and stereotyped components are merged indistinguishably.[1]

But such an account, while it might save the antithesis between the two categories on paper, would abolish it in fact, for a movement which has become confluent is no longer discrete, while one that takes on the qualities of fine usage and minute adjustment has surely ceased to be stereotyped.

The purpose of this argument is to suggest that (i) in such a familiar action as typewriting two separate categories of movement, discrete and stereotyped, cannot be distinguished, and that (ii) in respect of all the movements making up the total action we note an equal measure of precision, of fineness of adjustment and of capacity for variation.

It appears, therefore, that in our search for the discrete component in voluntary movement we shall have to abandon all the recognized meanings of this term, and to concentrate upon that emphasis on smallness that is a feature in the original usage of the term in physiology. For in this usage it is, indeed, the matter of size that is the significant one, *and the quality of separateness or non-confluence is almost* fortuitous, and dependent upon the fact that as a whole the musculature of the anæsthetized animal under experiment is inert. Herein is a point that seems to have been overlooked by those who have carried over the term "discrete" from

[1] How complex is the notion of "modulation" is best indicated by the following quotation (Tower, 1944, p. 170): "The phasic or episodic function (of the pyramidal tract) appears as a specific contribution to individual acts or performances, and often as the entire performance. This enters into all somatic motor activity of any complexity to initiate it or to speed initiation, to confer upon it adjustability in space, which is aim, and modifiability in time or in the course of execution. It contributes the elements of precision, lability, and finish to stereotyped performances. . . ." This is, indeed, a very striking passage, but, it may be submitted, it would prove extremely difficult to extract from it a clear idea in strictly scientific terms and in recognized physiological categories of the part played by the pyramidal system in the co-ordination of movement. To endow this system with the titles of a number of attributes, as is here done, is not to analyse or interpret its functions. How, for example, can stereotypy and lability inhere in the same movement? How can either quality inhere *in a single movement? Surely these terms do no more than express relations* of likeness and unlikeness between the component units of a sequence of movements. Indeed, it may be urged, that while this passage creates a very vivid impression in the reader's mind, it conveys no clear information.

the experimental laboratory to the study of voluntary movements.

Let us now take a movement instanced by Tower as a characteristic sample of the discrete movement, namely, the approximation of the tips of the thumb and index finger. Here would seem to be a movement as restricted as any to be found in the polymorphic range of voluntary motion in man, and one displaying maximal delicacy of adjustment.

If the observer, having completely bared his arm, holds his hand in front of himself and repeatedly makes the movement of bringing thumb and index finger tips together, he will be able, if the limb be sufficiently spare, to see in phasic action the muscles taking part in this "discrete" movement. He will observe that most of the muscles of the hand and forearm are taking part, and that when he makes the movement forcibly so as to bring the digit tips *into firm apposition, still more muscular action becomes* evident, although the range of the original willed movement has not increased. In this movement we see, also, that other digits than thumb and index are in motion. The middle and ring fingers show a synchronous flexion and extension of smaller range than index movement, but a motion quite incapable of being inhibited voluntarily. When the thumb-index apposition is forceful, the middle, ring and little fingers all go into synchronous flexion and extension. If now with thumb and index of his opposite hand the observer grasps the middle finger tip of the moving hand, he will feel as the rhythmic thumb-index apposition goes on that the middle finger strains to take part and cannot be induced to relax. In addition, muscles in the thenar eminence are seen to contract, the flexors and extensors of the digits in the forearm, and also the wrist extensors in phasic synergic action. In brief, we are dealing with a movement necessarily involving four or five digits, and, in the process, most of the musculature of hand and forearm, and the more we examine it the less discrete it is found to be. If, now, using this nipping movement of thumb and index, we proceed to pick in sequence, and out of a strip of cardboard in which they have been stuck in a row, a number of pins—beginning to right or left of the row and proceeding to the opposite end,

an inert musculature, for, as Sherrington (1946) has graphically expressed it, "to take a step is an affair, not of this or that limb solely, but of the total neuromuscular activity of the moment—not least of the head and neck." Hines has put the matter equally forcefully when she says "no violin or piano was ever played with the fingers and hand alone." Nor is all this implied background of movement to be disposed of as merely postural, as providing a medium against which the phasic movement stands out discretely, as it were. The illustrations given earlier in this paper show that this is not wholly so. Thus, the carrying over of the term "discrete movement" from the laboratory to the description of voluntary movement is invalid, for the term is inapplicable within this category of movement, and thus cannot be made the basis of a hypothesis of pyramidal system activities in movement. In addition, we have to stress the need not only of a precise, and precisely used, scientific terminology, but also that of distinguishing between abstract ideas and natural phenomena in our analysis, *classification and interpretation of the latter. In so far as* voluntary movement is concerned, the discrete movement is, I submit, a reified abstraction and not a natural phenomenon. It cannot therefore be a specific function of the pyramidal system to innervate discrete movements.

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On the Rôle of the Pyramidal System in Willed Movements

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SYNOPSIS

Chapter V

On the Rôle of the Pyramidal System in Willed Movements[1]

> *"In dealing with theoretical considerations concerned with the physiology of the nervous system, one is exceptionally liable to be misled by preconceived or introspectively evolved notions. . . . Symmetry and the desire for classification are apt to be mistaken for physiological principles and we tend to drift into the error of supposing that conceptions that are clear cut, easily comprehensible and 'reasonable,' acquire by that very fact an increased probability of being accurate expositions of the physiological processes they profess to explain . . . physiological necessity is apt to defy our preconceived notions of reasonableness and to escape any classification which is more respectful of logic than of fact."*
> —Wilfred Trotter, 1913, *J. f. Psychol. u. Neurol.*, 20, 123

That before a gathering of physicians I should propose to deal with the physiology of the pyramidal system may seem to call for some apology from me, yet, though what I shall have to say may well be of less importance than this meeting deserves, the choice itself can, I submit, be justified.

It is in the tradition of clinical neurology that it should maintain the closest association with the physiological study of the nervous system, and many are the noteworthy contributions to this science that clinical observation has made. Yet, there is a special justification for considering the rôle of the pyramidal system in willed movements, namely, that the human subject provides better opportunities for this study than does the animal in the experimental laboratory.

This may seem a surprising view, so modestly have we come to think of the clinical method in our time, but I am fortified in my belief by the following circumstance. When, recently, I began to put my ideas upon this subject in order, I ventured to mention my proposal to Sir Charles Sherrington, who replied to me: "You choose a hard question, and one which the bedside is far better placed to solve than is the laboratory, I think. The pyramidal system

[1] A paper read in abridged form before the Neurological Section of the International Conference of Physicians, London, September 1947.

is such a human feature." Thereupon he elaborated this theme with that insight into neural function we have come to regard as peculiarly the gift of this great physiologist.

There remains yet another advantage in the choice of the human subject and the clinical method, namely, that any study of disorders of willed movement from pyramidal lesion demands from the patient a degree of co-operation that no animal affords.[1]

These considerations, therefore, and others as good that could be adduced, are my apology for my subject to-day. It remains to ask how the problem is to be tackled. As clinicians we turn naturally to the observed phenomena of normal movement, and then to those of hemiplegia as the classic expression of pyramidal deficit : embracing in our survey hemiplegias of every degree of severity, hemiplegia with and without associated changes in muscle tone, hemiplegias from cortical and from subcortial lesions ; developing hemiplegia and recovering hemiplegia and so on. Again, we shall have to consider the recorded results of animal experiments : of cortical stimulations and ablations, and of sections of the medullary pyramid.

Definition of the Terms "Pyramidal" and "Extra-pyramidal" as applied to Neurone Systems

There can be few terms in neuro-anatomy and neurophysiology more in need of precise definition. A number of assumptions has grown up around both, the tacit acceptance of which has confused many a physiological exposition. Thus it was long taught that the pyramidal tract arose exclusively from the Betz or giant cells of the precentral convolution, and that the cells so named possessed an anatomical and physiological specificity.[2] Both assumptions are now at last dispelled, and, in their fall, have badly shaken those physiological hypotheses of motor cortical function which depended for a foundation upon

[1] For example, Sarah Tower (1940) speaks of "the limits set upon minuteness of examination by the unco-operative monkey," and again (1944) she notes that the hemiplegic chimpanzee after pyramidal lesions "is extraordinarily unstable in mood, swinging from unmanageable unco-operativeness to equally unmanageable co-operativeness."

[2] It is interesting to note that as long ago as 1881, Bevan Lewis, the pioneer of cortical cytoarchitectonics, expressed the view that the "giant cells" described by Betz did not constitute a specific morphological category, but were merely the largest representatives of a general formation of cells of wider distribution than Betz affirmed (*cf. Brain*, 4, 238).

their reality. This aspect of the problem of the identity of the pyramidal system has already been discussed by me elsewhere (Walshe, 1942 (*b*)), while Tower (1944) has summarized the latest details of the origin and constitution of the pyramidal tract. It is not necessary, therefore, to cover this ground anew. What is here referred to as the pyramidal system are those corticospinal fibres which arise from pyramidal cells in the fifth layer of the precentral cortex, and, traversing the medullary pyramid, decussate or remain uncrossed and make up the crossed and uncrossed pyramidal tracts respectively of the spinal cord. It is possible that these fibres in their course from cortex to medullary pyramid give off collaterals which establish anatomical connections and physiological relations with subcortical masses of grey matter. If this is so, then the pyramidal system below the medullary pyramid has a more restricted constitution than it has at higher levels.

It might follow from this that variations in range of function are involved: the higher part of the pyramidal system which contains fibres in addition to those which are corticospinal having a wider physiological rôle than that subserved by the latter fibres which constitute the medullary pyramid and the pyramidal tracts of the cord. To mention these possibilities is to indicate the incompleteness of our knowledge, not only of the physiology but even of the anatomy of the pyramidal system.

The term " extrapyramidal " though of comparatively modern origin has also had its vicissitudes, its referents being so often changed that it is now necessary to define it upon each occasion of use. In his classic paper on progressive lenticular degeneration, Kinnier Wilson used the term in connection with both afferent and efferent pathways including a cerebello-rubro-thalamo-cortical and a lenticulo-rubro-spinal path within the category of extrapyramidal pathways. In the early years of the century, Rothman appears to have used it for paths efferent from the cerebral cortex other than the pyramidal, but later, the term became restricted to certain subcortical efferent systems, namely, the basal ganglia and their projection paths. Its renewed extension to refer to pathways arising in, and efferent from, the precentral region of the cortex is a more recent development. *In the present paper the term " extrapyramidal " refers to efferent cortical neurone systems other than the pyramidal, and also to all subcortical efferent neurone systems that subserve movement.*

I.—Some General Principles of Study

Before we plunge *in medias res* and proceed to consider the relevant clinical and experimental data, let us for a few moments dwell upon some general principles that should govern our approach to the problem before us.

Whether of clinical or experimental origin our data are in large part the results of lesions of the nervous system, and it is essential to appreciate at the outset that the determination of normal function from the study of the symptoms of lesions is a very complex affair. The failure to grasp *this underlies the many unsatisfactory hypotheses of nervous* function that obtain currency. If, for example, tremor ensues upon a focal and destroying lesion of some part of the brain, we may not conclude that the function of the part destroyed was to inhibit tremor. It might be thought *that no one would propose so naïve a hypothesis, but it is* precisely this idea that was invoked by Ramsey Hunt (1917) to account for the tremor of the Parkinsonian syndrome. Nor was he in any way unique in his point of view, for speculations of this order abound in neurological *literature in respect of many encephalic structures and* their functions.

Many of us can recall those analyses of cerebellar ataxy that were current in the early years of this century, which proposed, on the one hand, that the atonia and asthenia of *cerebellar ataxy were due to loss of a normal tonic or sthenic* action of the cerebellum upon neuromuscular activity, while, on the other hand, the overshooting of the mark by the hand and arm of the ataxic subject when he stretched out to grasp some object, the so-called dysmetria, was attributed *to the loss of a normal "braking" action of the cerebellum* upon the same neuromuscular activity.

Nothing, indeed, could be easier than this facile *ad hoc* creation of a fresh function to explain each manifestation of disordered movement revealed by each different clinical test, but it is not physiology.

The inadequacy of the kind of symptom interpretation we have been discussing may perhaps be most clearly illustrated by a mechanical analogy, as apt in its way as an analogy can be. In the transmission system of a motor car, two toothed and bevelled wheels engage at right angles. If, as may happen, a tooth or cog on one of these wheels breaks off, at the point in each revolution at which the gap left by the lost cog meets the other wheel, there is a jar and a noise. We might therefore argue that since loss of a cog is followed by a noise, it was the "normal function" of that cog to prevent or "inhibit" the noise. The cog may

then be said to have a dual function : it transmits force and it inhibits noise—and our analogy is well-nigh perfect. Thus, baldly stated, the proposition is manifestly absurd, yet it typifies a line of thought to which the literature of neurology is no stranger.

It is clear, then, that such movements as we may observe after some component of the motor taxis of the organism is out of action, are the resultant, the sum, of the combined activity of the components that remain intact. For example, cerebellar ataxy is the disorder of willed movement which ensues upon a falling out of the cerebellar component and it expresses the activity of what is left of the neural mechanism —it is the product of the attempt at compensation for the lost component. This notion implies, in turn, that the intact mechanisms are themselves modified in their activity under these abnormal circumstances, and thus a fresh complicating factor is introduced in the attempt to infer the nature of cerebellar function from the observation of what is called, somewhat misleadingly, cerebellar ataxy.

It is this same order of complexity that must invest the attempt to deduce pyramidal functions from the observation of such willed movements as remain after pyramidal activity has been lost. It is many years since von Monakow (1917) emphasized the difficulty of "localizing function" from the study of the symptoms of lesions, and recently, Lashley (1937) has made it clear that this involves the use of intellectual processes somewhat more involved than those commonly thought sufficient to the task.

My second general point is this, that we shall do well to consider something of the circumstances in which the pyramidal system has evolved. I do not intend to embark upon an erudite phylogenetic or evolutionary study, but I believe that we may hope to get a lead as to the essential quality of pyramidal function by considering the place this system occupies in the human brain as evolved.

Seeking for some way out of that state of muddled suspense that is the first stage of thought upon any unresolved problem, I turned, as I have always turned, to Sherrington's "Integrative Action of the Nervous System," to find, as I have often found, what seems to me the point of view essential to the right approach.

In the illuminating ninth chapter of that magnificent book, entitled "The Physiological Position and Dominance of the Brain," there lie implicit, when not indeed explicit, the clues to the solution of many current problems of neurophysiology.

There we have presented to us a conception of the nervous system in which the entire edifice is reared upon two neurones, the afferent root cell and the efferent root cell. The two form the pillars of the fundamental reflex arc, and on the junction between them are superposed, mediately or immediately, all the other neural arcs, even those of the cerebral cortex itself.

It is the receptor neurone which is the driving force, and in particular the distance receptors that are the great "initiators of reaction." It is round the central endings of their afferent pathways that the cerebral cortex has been elaborated, and it is characteristic of the distance receptors that they tend to treat the musculature as a whole, and to engage it in long sequences of movement that are anticipatory of, and lead up to, later and consummatory events. In this task, the distance receptors have extensive internuncial paths, paths common to arcs that have arisen indirectly from receptors of various kinds. *The pyramidal tract is, on the efferent side, the principal path of this order, reaching its greatest importance in man.*

Thus we come to the idea of the pyramidal system as the path by way of which the receptors, in particular the distance receptors, can activate and direct movement. It is this notion of directing of movement that seems to me so essential to an appreciation of the rôle of the pyramidal system, and I cannot do better than to quote what Sherrington says in this matter, thus: "The series of actions of which the distance receptors initiate the earlier steps form series much longer than those initiated by the non-projicient. Their stages, moreover, continue to be guided by the projicient organs for a longer period between initiation and consummation. Thus in a positive phototropic reaction the eye continues to be the starting place of the excitation, and in many cases guides change in the direction not only of the eyeball but of the whole animal in locomotion. . . . The

mere length of their steps and the vicissitudes of relation between bodies in motion reacting on one another at a distance conspire to give to these precurrent reflexes a multiformity and a complexity unparalleled by the reflexes from the non-projicient receptors." Later, he says: " Locomotive progression and distance receptivity are two phenomena so fundamentally correlated that the physiology of neither can be comprehended without recognition of the correlation of the two."

Very recently the same theme has been taken up by Adrian (1947) in his Hughlings Jackson lecture, where he observes that " purposive acts, therefore, must be moulded like the movements of walking, by the controlling afferent patterns which are set up as the act progresses."

The words I wish especially to draw attention to here are the final ones, " set up as the act progresses."

Bartlett, also, in his recent Oliver-Sharpey Lectures on the measurement of human skill (1947) emphasizes the same point, saying " graded action, however simple it may be, has at least one of the fundamental marks of skill—an effector response is not merely set off by a receptor function but is guided and determined by it. The receptor functions that are important in the case of skilled behaviour . . . are always of that kind which claims to register something that is going on in the outside world. So they come to be particularly identified with the operations of the special senses, and especially of those distance receptors which are the basis of tremendous development of the central nervous system. Skill, then, whether bodily or mental, has from the beginning this character of being in touch with demands which come from the outside world."

The pyramidal system is the one through which this guidance is exercised, not in any capacity of initiator but *in that of an internuncial path.*

Germane to this view of pyramidal function are the many experiments that have shown how the cutting off of afferent impulses from the receptors profoundly reduces the spontaneous activity of the animal. Mettler (1935) and his co-workers found that the decorticated dog seemed unable to initiate movement or to cease a movement once

initiated, and they conclude that this initiating function is mediated by the pyramidal system. Bard and Rioch (1937) found the same lack of spontaneity in the decorticate cat, a lack in direct proportion to the loss of afferent pathways to the cortex. Other examples could be cited from the abundant literature on the subject.

We may therefore conclude that receptor activity, including both distance reception and proprioception, is so essentially correlated with pyramidal function that the physiology of the latter cannot be comprehended apart from the recognition of this correlation.

In all these circumstances it is, I submit, a fair criticism of much modern thought upon the excitable motor cortex and the pyramidal tract, based upon methods of stimulation, ablation and section, that it has considered both in so complete an isolation from the rest of the nervous system, that the essential importance of the sensory side of that system has been forgotten. Further, this abstraction of the part from the whole tends also to obscure the significance of the part abstracted, and in this instance has led directly to the attribution to the pyramidal system of functions which, as an internuncial system, it could not fulfil. Thus, Tower endows the pyramidal tract with "full responsibility" for the discrete control of movements, and holds that in virtue of its "discriminating qualities" it affords the cerebral cortex the latter's effectiveness as "an agent of choice." Surely, to take this view is to put the cart before the horse.

It is essential, therefore, to stress the importance of the idea of the receptor system as initiating and directing willed movements, in contrast to the widespread assumption that we may usefully contemplate the physiology of movement as starting *ab initio* from a mechanically conceived "keyboard" in the motor cortex. This point of view derives from a still earlier assumption, namely, that we may regard the highly artificial phenomena ensuing upon electrical stimulation of the cortex as reproducing the normal activity of the brain in initiating and directing willed movements, or at least as not differing from this in a degree or manner calling upon us for any intellectual exegesis. The willed movement, the "precurrent" reaction as it so commonly

is at its start, is not characteristically predetermined in form, duration or complexity, for it is moulded throughout its course by impulses deriving from the visual, extero-receptors and proprio-receptors. It is thus profoundly unlike the motor response to electrical stimulation of the cortex.

It would seem, therefore, that we may look upon the pyramidal *system as an internuncial, a common, pathway by which the sensory system initiates and continuously directs, in willed movements, the activities of the nervous motor mechanisms.* This sensory afflux is a condition of willed movement, and unless we consider both in association we cannot hope to see the purpose of either.

Having criticized some modern thinking upon pyramidal functions for considering these without due regard for what has been left out of the abstraction, it would ill become me to fall into the same error. This I should be doing were I to make no reference to the psychological considerations involved in the use of the term " willed " as applied to movement, and developed my argument as though willed movements were simply and immediately responses to sensory stimuli. An " educated skill," to use Bartlett's apt expression, is a psychophysical process or event, and between the impact of sensory impulses upon the cerebral sensory mechanisms and the motor reactions lie processes of choice, selection, judgment and timing which, while they have their concomitant physiological processes, belong also to the realm of the mind. There is motor behaviour, too, that, while its performance demands sensory direction, is initiated by no discoverable present sensory stimulus, but derives from mental processes.

It is not a part of this attempted formulation of an hypothesis of pyramidal function that I should even enter this complex and difficult field of discourse. Let it suffice that we recognize that in the definition just given of the rôle of the pyramidal system there has been omitted from explicit consideration the psychological aspects of what is involved in the term " willed " as applied to movements ; that but a fraction of the total problem of movement is being considered, and that we recognize that willed movement is not simply a response to sensory stimuli.

In the light of Sherrington's conception of the pyramidal system, *we may now see it in its due relation to the sensory* side of the nervous system. We can no longer continue to regard it as something enjoying a most unphysiological autonomy within the nervous system, nor as possessing "discriminating" functions which are the properties of synaptic fields but not of conductors.

II.—Hemiplegia as a Basis for the Study of Pyramidal Function

The value and the unique quality of hemiplegia in the human subject as the material of study in our present connection can hardly be over-estimated. They consist in the infinite gradations of defect of pyramidal function which hemiplegia presents to the clinical observer, in the slow recessions and the gradual developments of the state he may observe in his patients, in the stable residual states of all degrees of severity that are available, and finally in the degree of that essential co-operation between subject and observer upon which any refined analysis of willed movements must rest. In all these respects the clinician is more favourably placed than the experimental worker on animals, *whose lesions are all acute, whose ablations and sections are* irreversible, and whose subjects cannot really co-operate.[1] I suggest, therefore, to this audience of clinicians that we are in a unique position to contribute signally to the study of pyramidal function, and to have confidence in our findings as of crucial significance.

(i) *The Dual Character of Hemiplegia*

In considering whether we are to equate hemiplegia, as we encounter it clinically, with pure pyramidal defect, we have to remember that it includes not only loss of willed movements, but also, in most instances, numerous positive

[1] The experimental production of slowly progressive hemiplegia has not, as far as I am aware, been attempted, but there is a method by which it might possibly be achieved, namely, by implantation in some chosen site in the cerebral hemisphere of an animal, of a small hydatid cyst, which by its growth would reproduce the slowly progressive lesion of human pathology. It is conceivable that by some such means the range of physiological analysis of cerebral function by the experimental method might be extended.

or "release" manifestations, namely, increased tendon reflexes, clonus, hypertonus, and upon occasion the tonic neck reflexes of Magnus and de Kleijn (Simons, 1923; Walshe, 1923). When we consider the variability of these components, it is clear that for the clinician hemiplegia is far from being a uniform state. The question arises whether all these phenomena, negative and positive, are the consequences of abrogation of pyramidal action. Is it possible that some at least of the positive symptoms may be due to release of segmental motor mechanisms from the control of some other efferent path descending from the cortex, a path put out of action by the same lesion that has involved the pyramidal system? In other words, are two negative or destroying lesions concerned in the production of the typical residual spastic hemiplegia, one pyramidal the other extrapyramidal.

It was long assumed by clinical neurologists that pyramidal defect by itself accounted for all the phenomena of hemiplegia, negative and positive alike, and the dual character of hemiplegia was expressed in the simplest possible form of the familiar Jacksonian doctrine of release of function. Many years ago, however (1919), I suggested that we might have to modify this view, on the basis of certain clinical and experimental findings, and to entertain the possibility that negative lesions of two descending systems might be in question, that loss of movements might ensue from the pyramidal lesion and that some at least of the positive symptoms might express release of subordinate motor mechanisms from a second descending pathway and neuronal system.[1] By clinico-pathological study it has never been possible to resolve this uncertainty, for disease and injury in man do not provide us with clean sections of the medullary pyramids, and we have to allow that in all lesions producing

[1] From what has been said earlier of the possible difference in constitution of the pyramidal system above and below the level of the medullary pyramid, and also because "extrapyramidal" efferent fibres of motor function arise within the limits of the excitable motor cortex, it is clear that we cannot equate a lesion of the motor cortex with one of the pyramidal tract at or below the level of the medullary pyramid. Thus, three elements may be involved in a destroying lesion of the motor pathways between the pre-Rolandic cortex and the medullary pyramid, namely, direct corticospinal fibres, collaterals given off by corticospinal fibres, and extrapyramidal efferent fibres of cortical origin.

spastic paralysis, whether hemiplegia or paraplegia, it is possible that extrapyramidal as well as pyramidal fibres may be involved.

Further, clinical study has taught us (i) that there is in *hemiplegia no constant direct relation between the severity* of loss of willed movements and the degree of hypertonus present, (ii) that we frequently encounter marked increase of tendon-jerks where there is no unequivocal increase of tone, (iii) that associated movements (tonic reactions) are not seen save in the presence of marked hypertonus, and Magnus and de Kleijn tonic neck reflexes are not constantly, or even commonly, found, even in the presence of such a degree of hypertonus. That these components should show such variable relations to one another does point to the operation of more than a single factor in the production of the familiar picture of spastic residual hemiplegia, and thus far does support the speculation expressed by me in 1919.

We must turn, therefore, if we are to resolve this uncertainty, to those cases of experimentally caused hemiplegia in which the lesion is section of the medullary pyramid in cat, dog and monkey (Tower, 1935, 1940, 1944 ; Marshall, 1934 ; Ranson, 1936 ; Liddell and Phillips, 1944). In cat and dog there is some degree of increased tone of extensor incidence in the limb muscles. Tower describes this as "stiffness" but provides an argument, not easy to follow, for regarding this stiffness as being merely an absence of *flexor activity : thus preserving her thesis that the picture* of pyramidal lesion in the cat is a purely negative one. However, Marshall, Ranson, and Liddell and Phillips all agree that hypertonus is a constant feature of pure pyramidal section in cat and dog.

In answer to the question: "Is the syndrome of pyramidal defect one of purely negative character without any release phenomena in the case of monkey and chimpanzee?" Tower replies with a categorical affirmative. "In the realm of motor function," *she reports*, "*the condition is unquestionably* one of deficient function, without phenomena of release," and putting the matter conversely, says, "there is no evidence of inhibitory function" of the pyramidal system.

As in the case of her study of the cat, however, this conclusion is not quite in accordance with the facts she describes, for she records a proprioceptive grasp reflex in both monkey and chimpanzee (" emphatic " in the latter) and a Babinski plantar response in the chimpanzee.

Now if, as is generally agreed, we regard the tonic grasp reflex as a proprioceptive reaction (Walshe and Robertson, 1933 ; Walshe and Hunt, 1936), and the Babinski plantar response as an integral part of a phasic nociceptive flexion reflex (Walshe, 1915), then we have as a sequel to a pure destroying lesion of the pyramidal system in these animals release manifestations in both the tonic and the phasic fields of motor reaction. Further, Tower reports that in the hypotonic musculature of the hemiplegic monkey, tone is influenced by posture, and is increased in the anti-gravity muscles when the animal is standing. How this variation is to be accounted for if not by tonic reflexes of the order described by Magnus and de Kleijn is not clear, and these must surely be release phenomena.

It is surprising in these circumstances to find Denny-Brown (1945) observing that " the final blow to the clinical conception of disorder of the 'pyramidal system' was delivered by Sarah Tower in her classic description of the monkey after section of the pyramid in the medulla."

Plainly the obituary is premature, for the evidence remains in favour of a dual symptomatology in hemiplegia due to pure pyramidal lesion, though it does not exclude the possibility that *some part* of the positive manifestations may be due to release from the control of extrapyramidal systems of cortical origin. Further, the view that the pyramidal system has no function of control or inhibition makes it difficult to understand how it can play the very complex rôle imputed to it. Lloyd (1941) has provided direct evidence of reciprocal innervation (excitation and inhibition) of internuncial neurones in the grey matter of the spinal cord by impulses descending the pyramidal tract. Denny-Brown (*loc. cit.*) also, paradoxically enough, has given cogent reasons in favour of the exercise of such functions by the pyramidal system, and to these we shall later return.

(ii) *The Loss of Willed Movements in Hemiplegia*

Our purpose being to consider the rôle of the pyramidal system in the innervation of willed movements, we may leave the question of the positive or release symptoms which we must, however, still regard as an essential item in the total picture of loss of pyramidal function.

(a) *Pyramidal Lesion in Monkey and Chimpanzee*

It would take us too far afield to describe the various states of loss of movement resulting from pyramidal lesion throughout the wide range of animals from cat to anthropoid, and I propose, therefore, to concentrate upon Tower's (1940, 1944) account of the loss of movement seen in monkey and chimpanzee after section of the medullary pyramid. No available account compares with this in detail and completeness, or in the precision with which the lesion was produced and anatomically controlled. Subsequently, I shall seek to elicit from the disturbances of the upper limb in clinically observed hemiplegia, some of the principles illustrated by pyramidal defect in man.

I confess to a difficulty in summarizing the facts of observation recorded by Tower, because she has embodied her account in a terminology that presupposes the theoretical conclusions she proceeds to draw, and fact and hypothesis are thus not always easy to differentiate. This gives in places an appearance of inconsistency in the description. Thus she finds that there is diminished general usage and loss of initiative in all the limb movements, and such movements as are retained are weak and often tremulous, inaccurate, incapable of modification while in progress, call for prodigious effort and lead to excessive fatigue. It would appear, therefore, that there is no order or aspect of willed movement that is not gravely impaired. In addition, hopping and placing reactions of the lower limbs are abolished. However, this gross affection of willed movements is selective, for while digital movements are totally abolished, movements leading to assumption and maintenance of postures, reaching and grasping movements persist. They are even said to " function well," but in what sense is not

clear in view of what has already been said of their state of efficiency. Nevertheless, an antithesis begins to be developed between these two categories of movement, the former being "sharply discriminated against" by pyramidal lesion and "selectively destroyed." In the plain terms of description as given by Tower, this antithesis is not so readily apparent. Yet it is further developed in the final formulation of pyramidal function, and comes to dominate the hypothesis ultimately propounded. Thus, the unique rôle of the pyramidal system is the initiation and control of discrete *movements, especially those of the digits. Secondly, it* "enters into all somatic motor activity of any complexity to confer upon the stereotyped extrapyramidal performances adjustability in space, modifiability in the course of execution, and all modulations of pattern which make for aim, accuracy, economy, lability and finish" (1940, p. 87). Thirdly, by its tonic function it provides for smooth and continuous action. Fourthly, it shows no sign of inhibitory activity.

Willed movements are thus deemed to fall naturally into two categories, in respect both of their characters and of their anatomical substrata. There is a category of "discrete" movements pyramidally initiated and controlled, and one of "stereotyped" movements extrapyramidally initiated and controlled. Not only is this second category "stereotyped," but it lacks qualities of adjustability, modifiability, accuracy, aim, lability and finish. These qualities, in the normal motions of the intact animal, are "conferred" upon it by the "modulating" action of the pyramidal system. It is important, if we are to understand the essential nature of Tower's hypothesis, to bear this curious relationship of pyramidal to extrapyramidal components in willed movement in mind.

In a recent paper (Walshe, 1947) I have discussed the ambiguous nature and usage of the terms "discrete" and "stereotyped," and the fact that once these are given definition they are found unsuitable to any classification of willed movements and do not provide a true antithesis.

What is more important is that we have here a conception of central nervous activity that it is difficult to accept. The

attachment of the two hypothetical categories of movement, discrete and stereotyped, to separate anatomical structures, the pyramidal and extrapyramidal systems respectively, necessarily involves certain corollaries. *Ex hypothesi*, extrapyramidal components of willed movements lack aim, accuracy, etc., and thus we find ourselves once more with a "protopathic nervous system" in replica, with its own peculiar physiological properties and shortcomings and its own distinct anatomical substratum, the extrapyramidal system. Set over it we have the pyramidal system which has not only its own specific function of initiating "discrete" movements, but a secondary function of conferring upon the crude activities of the extrapyramidal system those high-grade qualities it lacks. For "pyramidal" write "epicritic" and the analogy with Head's conception of the afferent nervous system is complete.

Now it is surely not to be disputed that pyramidal and extrapyramidal systems are both in action in, and are essential to, all possible willed movements, but their respective rôles cannot be generalized within the limits of this physiologically unreal scheme which pictures a type of nervous system that nature has never presented to our gaze (*cf.* Walshe, 1942 (*a*)).

It is difficult to believe in an extrapyramidal motor system so evolved that, left to itself, it functions without economy, accuracy, aim or finish. On the contrary, we know that when acting in reflex fashion the complex arcs of cord and brain-stem do not so behave, but show a beautiful precision and adaptation. It is their nature to do so, nor in these circumstances do they owe anything to the activity of the pyramidal system. Further, there are various features of pyramidal deficit that do not tally with the hypothesis. Thus, hopping and placing reactions are surely not discrete, and they form a stereotyped pattern. Yet they are completely abolished by pyramidal section.

(b) *Defect and Loss of Willed Movements in Clinically Observed Hemiplegia*

Compared with the relative uniformity of its experimentally produced counterpart, hemiplegia as seen in the

human subject is a thing of almost infinite variety within the wide range of its extreme manifestations, and it presents unique opportunities for the observation of the evolution and dissolution of motor function as we study recovering or developing hemiplegias and all grades of stable residual weakness. To be familiar with all this is indeed to have a liberal education in clinical neurology.

To seek to describe or even to enumerate all the defects of movement to be seen in these circumstances would be a task beyond the scope of the present occasion. I believe it unnecessary for me even to attempt it, because the general features of the loss of movements characteristic of hemiplegia are sufficiently revealed by a study of the hand and arm in a subacutely or slowly developing hemiplegia.

In the upper limb the paresis first appears in the movements of the hand and digits, and then spreads to involve the limb in a central direction and in that " compound order " of paralysis long ago described by Jackson, and familiar to every neurologist.

Three features are to be noted in this process : the *number* of movements normally possible is progressively lessened, and this involves a marked diminution of the *variety* of possible movements because many of these are combinations and sequences of smaller movements. Thus compound movements of the hand and digits weaken, dwindle and disappear early. Secondly, all movements become markedly slow in initiation and performance, and thirdly, such capacity as is normally possessed to move digits individually lessens progressively. The progressive diminution of the number of possible movements necessarily leads to a greater uniformity of pattern of hand movements, and this we might speak of as an approach to stereotypy in the hand's activities, but this, be it noted, is a very different thing from the statement that discrete and variable movements disappear and leave a separate category of stereotyped movements ; such a summary would be a travesty of what is actually happening.

In view of what has been said earlier of the existence of a specific category of discrete movements, it is necessary to be explicit as to what may be seen as the hand weakens with

the development of hemiplegia. Few, if any, of us possess the power to move one digit only at a time. Even in the familiar gesture of beckoning, the appearance of discreteness is illusory, for we normally fix the other digits by firmly flexing them into the palm and then closing the flexed and opposed thumb over them. Even so, the thumb and digits can be felt to contract concurrently with the index, and if we try to beckon with the index while the thumb and other digits are open, we see them all enter into the movement and we are wholly unable to inhibit their participation. Even the simple movement of alternate flexion and extension of a digit is always accompanied by a similar movement of lesser range by its fellows. In short, a discrete movement of a single digit is a feat none of us is capable of. What happens as hemiparesis develops is that we become *less able* to move the digits differentially, but the change is one of degree and not one of kind.

Undoubtedly the first group of movements to disappear are those in which the interossei, lumbricales and the flexors and opposers of the thumb engage. Abduction of the fingers and extension of the phalanges are earlier and more severely affected than adduction. As this occurs, the combinations of flexion, extension, adduction and abduction are lost and the hand is at once severely disabled, for these are the movements that give the hand as a whole its wide range of rapid movements. This is easily seen by the simple test of asking the patient to touch each finger tip in succession to the tip of the thumb, beginning either with index or with little finger. There is a stage at which, while the necessary flexion of each digit remains, the necessary adduction and apposition are lost and the thumb and finger tips are not approximated, but flex futilely into the palm.

In short, the hand and digits and after them the forearm, arm and limb girdle are progressively denuded of movements, and with this impoverishment, the range and variety of mobility necessarily lessens, for the elements out of which the normal combinations and sequences of movement consist are not there.

Thus it is that the wider and the more complex the combinations and sequences that go to make up a given willed

act, the more gravely its execution is impaired. Further, since from its very structure the hand is capable of a wider range of different movements than are possible in the proximal segments of the limb, it is the hand that exhibits most profoundly the consequences of defect in pyramidal function.

An equally striking feature of the situation we are considering is the very marked delay in starting and the slowness in performing the movements that remain possible in the affected hand and arm. In his famous Bridgewater Treatise (1829) on "The Hand : Its Mechanism and Vital Endowments," Sir Charles Bell discusses the relations of power and velocity of movement in muscles, pointing out that the small hand muscles are characterized in action by their velocity rather than by their power, the proximal muscles by their power rather than by velocity of contraction. He says : "The same interchange of power for velocity, which takes place in the arm, adapts a man's hand and fingers to a thousand arts, requiring quick or lively movements . . . these small muscles (interossei and lumbricales) *attached to the near extremities of the bones of the fingers* where they form the first joint, being inserted near the centre of motion move the ends of the fingers with great velocity. They are the organs which give the hand the power of spinning, weaving, engraving ; and as they produce the quick motions of the musician's fingers they are called by the anatomists *fidicinales*."

Although, therefore, in the paretic arm the movements that are left are naturally the slowest, there is undoubtedly a marked slowing down even of finger movements when any remain, and this is associated with every evidence of great effort on the part of the subject and of rapid fatigue when such weak slow movements are persisted in.

This brief sketch of the sequence of events when loss of pyramidal function evolves slowly in a part particularly under its influence may be resolved into certain elements : (i) There is a slowly progressive waning and disappearance of movements, beginning in hand and digits and spreading proximally up the limb in a central direction and in compound order. Ultimately, there may be no movements

that are not lost, but there is an intermediate stage at which some movements of every part of the limb are lost. As the number of retained movements dwindles, the motions of the limb as a whole, or of the hand considered separately, tend to become more uniform, until with profound reduction so few movements are left that the *patterns of movement* left qualify for the term "stereotyped." However, this is not because a specific category of stereotyped movements is left uncovered in its native imperfections by the loss of a different category of "discrete usage," but simply because when only one or two movements remain there can be no variety. (ii) From the structural qualities of the hand it possesses a greater number and variety of movements, and of quicker movements, than the proximal parts of the limb, and in the characteristic evolution of paralysis, the movements of the leading part, the hand and fingers, suffer first and most severely. (iii) There is great and increasing slowness of movements.

I do not find it possible to generalize this state of affairs in terms of a differential effect upon two distinguishable categories of observed movement, discrete and stereotyped, the one being lost and the other intact but lacking refinement by the category lost. Not only is there a loss of relatively simple movements which is maximal at the distal part of the limb, but there is strikingly a loss also of those long complex movement sequences, of those precurrent or anticipatory motions, that employ the musculature of the limb as a whole, that is, in the fashion in which it is normally employed in willed motion. Initiation and direction of movement are both impaired or lost because the internuncial path by which travel the impulses that should mediate these functions is interrupted. Sensory impulses reach the cortex and are therein integrated and their psychical concomitants in consciousness are intact, but *the way out* for the activating and directing impulses from motor cortex to subordinate motor centres and ultimately to the final common path is blocked. Every form of willed movements suffers accordingly.

III.—The Rôle of the Pyramidal System in Willed Movements

The inference with which we started, one taken from Sherrington's "Integrative Action," is that we should regard the pyramidal system as an internuncial one, a sort of common path standing between the receptors, the distance receptors being dominant, and the motor mechanisms of the nervous system. The distance receptors are the great initiators and directors of all those sequences of willed movement, simple and complex, short and long, anticipatory and consummatory, that compose the willed mobility of the intact individual.

This mobility involves what Jackson spoke of as co-ordination in space and co-ordination in time, and for purposes of analysis it is necessary to think of these two aspects of a single function in separation, remembering always that they are not separated in action. Jackson's aphorism in which he speaks of the two as, respectively, the harmony and the melody of movement aptly expresses the relation and the natural unity of the two.[1]

Now co-ordination in time, that is, the ordered sequence of movements, must surely be intimately dependent upon sensory direction, while co-ordination in space, that is, the composition of movement at any given moment, has to be thought of as closely dependent also upon the patterns of movement laid down in the cortex.

This point of view reveals another aspect of our problem, namely, whether it is an adequate conception of pyramidal function to think of the system as simply internuncial. Does it not, must it not, play some more complex rôle in co-ordination in space than this view allows? This in turn raises the larger question of the rôle of the pyramidal system within that physiological entity we speak of as the motor cortex, and to this we must now give some attention.

[1] In a very suggestive article Lashley (1937) has given reasons for thinking that co-ordination in time and co-ordination in space represent different types of integration, calling for different mechanisms of organization in the cerebral cortex, and thus for spatial separation of the fields in which the different processes operate.

(i) *The Relation of Pyramidal System to Motor Cortex*

The controversies and the wide differences of opinion as to the rôle and constitution of the motor cortex which have characterized the relevant literature during recent years (*cf.* Walsh, 1942 (*b*)) depend upon something more fundamental than differences about the meaning of words, though these have played a large part, and they indicate a general failure since the time of Jackson to grasp all the implications of the cortical control of movement. For example, what is the relation between the motor cortex and that forward lying cortical region whose functions we may speak of as eupraxic, that is, what is the relation between Jackson's middle and highest levels? What is the precise rôle of the pyramidal system of neurones within the motor cortex, and are they right who assume, as some appear to do, that the cells of origin of the pyramidal tract constitute the entire motor cortex?

For some years an influential body of opinion has equated the cells of origin of the pyramidal system with the motor cortex, and has further restricted this by assuming that only the so-called "giant cells" of Betz give rise to pyramidal fibres. Though this hypothesis has not been explicitly disavowed by its proponents, it is not likely that they would now seek to sustain it. Nevertheless, hypotheses of this order become fixed in the relevant literature and continue to influence thought long after they are found to be inadequate. It is clear, therefore, that as long as we continue to regard the giant cells as the sole cells of origin of the pyramidal tract, and equate them with a "histologically defined" motor cortex (Fulton, 1933), we cannot possibly begin to think of the pyramidal system as simply an internuncial one.

But the facts require that, and the time has come when, we must abandon this point of view with the anatomical fallacies upon which it was based, and seek some wider generalization of the rôle and constitution of the motor cortex and of the pyramidal system. While the latter is plainly the main projection path of the former, I submit that we err when we assume that the cells of origin of the

pyramidal tract, however widely we now know them to be distributed, make up the motor cortex *in toto*. Yet implicitly, when not explicitly, this is, in fact, what we have commonly assumed.

It is not within the scope of my present limited task to generalize the entire motor functions of the frontal cortex, but the main outlines of what, following Hughlings Jackson, I conceive these functions to be will serve to orientate my hypothesis of pyramidal system functions.

It is clear that however widely Jackson's views on the organization of the excitable motor cortex, his "middle level," may have influenced neurological thought in our time, his conception of the "highest level" of motor integration has not influenced it at all. Thus, the final representation of "educated skills," the function of eupraxia as it may be called, is on Jackson's hypothesis laid down in the frontal cortex anterior to the excitable motor cortex. Yet, for many years, following Liepmann's famous exposition, we have thought of apraxia, that is, of disorders of eupraxia, as solely associated with lesions of the supramarginal gyrus—though Liepmann was never so exclusive—and we have been content with more or less conventional classifications of apraxia, *e.g.*, ideational, motor, etc. These disturbances are now, indeed, commonly spoken of as indicative of a lesion of the supramarginal gyrus, or of subcortical paths leading from it to the precentral gyrus and via the corpus callosum to the crossed precentral cortex. Yet, with some inconsequence, we continue to regard motor or expressive aphasia and agraphia as forms of apraxia involving articulate and written speech and to associate specific losses of these skills with lesions of the frontal cortex. It may be questioned whether lesions of the supramarginal gyrus and of paths leading from it ever yield the isolated loss of some specific "educated skill" such as we see in expressive aphasia, other skills being left intact, and it is clear that there are problems involved in this question of the highest level of physiological integration of movement that have scarcely yet been recognized. But it is not my task to discuss this subject further now, and the proposition I submit is that whatever disorders of eupraxia may ensue upon lesions of

the parietal cortex, there is, in fact, a representation of educated skills in the frontal cortex, a representation which constitutes Jackson's "highest level."[1] The functions of this are not to be conceived as of the mere building up *ad hoc* of learned movement-complexes, from elementary units of movement represented in the precentral gyrus. Its rôle is that of a true representation of those large and infinitely complex movements that, following Bartlett, we can speak of as educated skills, and since these of their nature involve long sequences of movement, it may well be, as Lashley (*loc. cit.*) has suggested, that temporal co-ordination, co-ordination in time, is the essential integrative mechanism subserved by this level. To seek to name in morphological terminology the precise topography of this representation within the frontal cortex would be to pretend to that figmental precision that is the major and vitiating error of modern cortical cytoarchitectonics (*cf.* Lashley and Clark, 1946).

A destroying lesion of this anatomical substratum of the eupraxic mechanism abolishes the willed initiation and performance of one or more "skills," while leaving unimpaired the willed performance of other skills even though these may employ some or all of the muscles engaged in the now lost skills. The abolition of such a skill, which may range in complexity from articulate speech to the appropriate handling of some familiar tool, we speak of as "motor apraxia."

It is, of course, probable that there are many as yet unidentified expressions of negative lesions of the frontal eupraxic mechanism: for example, the striking general immobility and lack of initiative of some cases of frontal lobe neoplasm may be a generalized highest level paralysis of almost all skilled usages of the musculature, for this level does tend to engage the musculature as a whole.

More familiar to us are the effects of destroying lesions of the middle level, the motor cortex. Here also movements are lost while other movements employing some or all of the muscles engaged in the lost movements remain intact.

[1] There is some experimental evidence suggesting that a motor apraxia ensues in the monkey upon ablation of the so-called "premotor" cortex (*cf.* Jacobsen, 1932, *Proc. Ass. Res. Nerv. and Ment. Dis.*, 13, 225).

The movements lost are of a simpler order than the "educated skills" we have been considering. The latter also, however, must suffer disorder from a middle level lesion because this level and its projection path link the eupraxic mechanism mediately with the musculature, but this disorder is not a specific paralysis of a skill such as characterizes a highest level lesion. In neither case, be it noted, can we rightly speak of a paralysis of muscles: a point to which we will return later.

We have, therefore, in these two physiological levels two orders of representation, both necessarily employing the pyramidal system; the highest level mediately, the middle level immediately. The sensory afflux we may regard as acting immediately upon the highest level, and only indirectly and through this upon the middle level.

Experimental evidence suggests that the electrical excitability of the motor cortex depends upon cells that lie in the same fifth cortical layer wherein the cells of origin of the pyramidal tract are to be found, but this does not allow us to equate the motor cortex with these cells, and I submit that they are in all probability simply that part of the motor cortex considered as a physiological unit which constitutes the "way out," and that, in their larger relations, they form with their axones that internuncial system Sherrington originally designated them.

(ii) *The Relation of Pyramidal System to Subordinate Motor Mechanisms*

We return, then, to our first conception of the pyramidal system as an internuncial one employed by the receptor system in the activation and direction of willed movements. A great deal is now known of the motor mechanisms which, through the medium of the pyramidal system, the receptors activate and control. The work of Magnus and his school, building upon foundations so securely laid by Sherrington, has revealed what the neuraxis is capable of in co-ordination of movements and of postures, and we know something, too, though not yet all, of the rôle of the neo-cerebellum—an organ that is essential to the perfect activation of the

segmental motor machine in willed movements (Walshe, 1927).

Comparative physiology has also taught us how, as the animal phylum is ascended, the segmental machine becomes more and more dependent upon activation from the cerebral cortex and the profoundly immobile, helpless state of the monkey after bilateral pyramidal section reveals the measure of this dependence.

So far nothing has been said of the "how" of this activation and direction. The notion of control of lower levels by higher is fundamental in the Jacksonian conception of evolution in the nervous system, and control necessarily involves inhibition as well as excitation. Yet Tower has presented us with an hypothesis of pyramidal activity in which inhibition is excluded. Since she speaks (1936) of "fractionation" of complex synergies as a primary pyramidal function it is difficult to see how inhibition can be excluded from the operative processes concerned.

Denny-Brown (loc. cit.) has recently drawn attention to some observations of Coghill that are germane to the subject, showing how the development of segmental or local reactions may be arrived at by the fractionation of earlier developed general patterns. Such a mode of evolution of function involves inhibition as a prime factor. It involves the isolation of a movement by the inhibition of the other elements in the original pattern: a "differentiation by exclusion" as Denny-Brown expresses it, adding that "a cortical movement in such a conception would require a widespread inhibitory counterpart over all other postural or progressive reaction except that which aids and augments the action desired."

However, when we recall the infinite complexity of willed movement patterns, it seems unlikely that differentiation by fractionation can by itself be adequate. At most it can be little more than a necessary preliminary to differentiation by combination (spatial and temporal), and this notion brings us near Leyton and Sherrington's classic *interpretation of the functions of the excitable motor cortex.* What I am proposing is the idea of the cerebral cortex, sensory, eupraxic and motor, the seat of a constantly changing flux of excitation patterns, using the pyramidal system as the

pathway by means of which it achieves a fractionation and combination (in time and in space), by processes of selective inhibition and excitation of bulbospinal motor mechanisms, of those reflex synergies that the experimental study of the variously truncated nervous system has revealed to us in such abundance. By this process of fractionation and combination there is woven the complex and constantly varying patterns of willed movement.

In acting as the agent of this process the pyramidal system is passive in the sense that it is driven by the receptors through the cortex. This process of driving is what Bartlett (*loc. cit.*) expresses as the " simple and basic fact of detailed determination by receptor function " ; a function which involves the integration of all sensory sources and provides the basis of spatial and temporal co-ordination, whether of large movements or of small.

But no hypothesis can leave out of account the rôle of basal ganglia and cerebellum in the formation of willed movements. It is specifically in relation to willed movements that the neo-cerebellum acts, for the reflex reactions of the thalamus animal are not impaired by ablation of the cerebellum, and cerebellar ataxy is essentially a disorder of willed movements (Walshe, 1927).[1] Nevertheless, precisely how cerebellum and pyramidal system collaborate remains unknown. In a still deeper obscurity lies the rôle of the basal ganglia. No specific contribution to willed movement, or even to the complex reflex reactions of the neuraxis, has so far been conclusively apportioned to them. In the circumstances, speculations abound, but as they add nothing to our knowledge of pyramidal function it is not relevant to discuss them. Therefore, any present attempt at a comprehensive view of the functional relations of the pyramidal system must suffer from gaps in our knowledge, the importance of which it is difficult to assess.

It is now possible to correlate in broad terms the results of a destroying lesion of the pyramidal system with the views

[1] This statement should, perhaps, be qualified to this extent, that the tendon jerks in the subjects of a destroying lesion of the cerebellum—the cerebral hemispheres being intact and the power of voluntary movement not abolished —do show characteristic alterations in form and time relations (Holmes, 1917, 1939).

of the functions of this system which have been sketched. It is reasonable to expect that willed movements will fail *in proportion as the activating influence of the receptors*, the distance receptors in particular, upon the motor mechanisms fails to reach these through the pyramidal tract. The failure will be selective where pyramidal activity is impaired rather than wholly lost, involving most severely the most complex and long lasting movements which are most dependent upon continuous sensory guidance. These will be movements of what Jackson spoke of as the leading parts. Thus, the arm and hand, that "delicate explorer *of space in manifold directions," may be expected to show* a greater disablement of its activities than the lower limb with its far more limited repertoire of movements and their more deeply impressed organization in the motor centres.

This selectivity we should expect to find one of degree rather than one of kind, governed rather by considerations of complexity than of mere size of movements.

Further, with impaired direction, such movement sequences as persist will not vary during execution to adjust to what Sherrington speaks of as "the vicissitudes of relation between bodies in motion reacting on one another at a distance."

All these defects are, indeed, what we have found to be characteristic of the paralysis following pyramidal lesion.

(iii) *The Relation of Pyramidal System to Musculature*

Finally, one more point calls for mention in any discussion of pyramidal function. The pyramidal tract is the projection path of the motor cortex, and we know that there are two views of the physiological organization of the latter: the generally accepted view that the representation is one of movements, and the newer view of Foerster (1931), Fulton (1936), and Hines (1944), that the representation is one of single muscles. If we accept the latter view we should surely have to hold also that the pyramidal tract innervates muscles as such, and that pyramidal defect must show itself as a paralysis of muscles rather than of movements. Indeed, Foerster has not hesitated to commit himself to the statement

that he has seen an isolated paralysis of a single muscle from a cortical lesion. No other clinician, I think, has ever made such a claim, which, as every student of Beevor's exhaustive studies on this subject knows, is directly opposed to all clinical experience. Finally, also, Lloyd's (1941) account of the spinal mechanism of the pyramidal system in cats affords no support to any hypothesis of a direct innervation of "single muscles" by this system, but does provide evidence incompatible with it.

In conclusion, as I realize full well, this paper is no more than an adumbration, a sketch, of a theory of pyramidal functions expressing a point of view for which the most I claim is that it is an attempt to go back forty years to the philosophical principles enunciated in Sherrington's "Integrative Action," and to those, still more remote, enunciated by Jackson ; principles somewhat lost sight of in the years that have followed. It is also a point of view that, I believe, contains nothing contrary to the known principles of neural function, and one which does not involve that incautious use of abstractions which has tended to obscure the great merits of Sarah Tower's exhaustive study of pyramidal lesion in monkey and chimpanzee ; a study which, when reinterpreted, must prove of high value in the solution of the difficult problems of pyramidal function.

IV.—Summary

The pyramidal tract is an internuncial path, a common path, standing between the massed receptors on the one hand and the motor mechanisms of the nervous system on the other. It has evolved in particular relation to the development of the distance receptors, perhaps vision alone, and has reached its highest importance in man. It is the path by way of which the distance receptors put the motor mechanisms of the nervous system in operation ; activate, and thereafter direct their action throughout the performance of those sequences of willed movement, short and long, simple and complex, characteristic of the normal organism. *The pyramidal system of itself initiates nothing,*

and to speak of it as "responsible for" this or that category of movements is to ignore the source and motive power of its activities. It is simply the channel through which pass the impulse volleys by which willed movement is activated and continuously moulded by controlling cortical afferent patterns of excitation. If this be so, then it is concerned with all possible willed movements, and all aspects of willed movement, and if, as has been postulated, the cortex by way of the pyramidal system fractionates and then combines the functional elements of reflex segmental mechanisms, then every willed movement, short and long, small and large, restricted and ample, is as wholly pyramidal as it is extrapyramidal, and separate categories of movement thus anatomically classified or grouped as discrete or stereotyped have no existence as phenomena ; they are abstractions not discernible as things or events in nature.

The conception of pyramidal function now so widely current has three grave defects : it overlooks the simple and basic fact of detailed determination by receptor function, and treats the sensory system as irrelevant ; it fails to appreciate that the distance receptors, of which the pyramidal system is the agent, tend characteristically to employ the musculature as a whole rather than in anything that can accurately be called discrete movements ; and, thirdly, by implying an equation between the cerebral motor cortex and the cells of origin of the pyramidal tract, it is forced to attribute to the pyramidal system functions far beyond those of its real rôle as an internuncial path.

Precisely how the pyramidal system, or rather the cerebral motor cortex, and the neo-cerebellum are related remains obscure, but that the activity of the latter is essential to the co-ordination of willed movements, and that this is its main function, is clear.

Finally, a neurone system fulfilling the rôle here attributed to the pyramidal system must surely be the medium of inhibition as one mode of control of subordinate motor mechanisms. If this be so, than a corollary of loss of pyramidal action is a dual picture with positive and negative elements. In fact, in both the phasic and tonic fields of motor reaction there is clear evidence of positive or release

symptoms. It seems certain, for example, that the spinal flexion reflex, of which the Babinski plantar response is an integral part, is to be so regarded, while in the tonic field indications are not lacking that here also release of function is part of the picture of pyramidal defect.

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The Integration of Medicine

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Chapter VI

The Integration of Medicine [1]

In the course of discussions upon the future and development of medicine two themes recur with melancholy iteration—namely, that specialism is an evil, and that it is inevitable. For this dilemma in which it seems generally agreed that we find ourselves no one proposes a remedy, or lights the path we must follow if we are to discover one. In his Harveian Oration of 1931, before the Royal College of Physicians, Sir Robert Hutchison spoke with insight into our situation when he said, "Specialism is inevitable; but though favourable to the accumulation of facts, it is bad for the philosophy of knowledge. There is too little speculation and too little use of the imagination; and most scientific literature is barren in ideas." Therein he put his finger upon a malady of modern science.

Yet, whether the remedy the Harveian orator proposed is one we can adopt is open to question, for he went on to say that "it might be a good thing if there were a close time in laboratory work, say, for five years, to enable us to digest the vast accumulation of knowledge we already possess and to think out new lines of advance." Yet I doubt if in the present climate of opinion, five years of research inactivity would increase interest in the use of the intellect, while, on the other hand, if we could stimulate this interest, a five-year truce with facts would be neither necessary nor desirable. The average modern scientific worker, paradoxical as the suggestion may seem, is more apt to be a man of action than of thought. He tends to distrust ideas. He has not always learned to achieve a harmony of observation and of general thought. His output of facts is necessarily reduced if he pauses to think about them. It may then easily be said of him that he is not making "discoveries" as fast as

[1] Being an abridgment of the Annual Oration of the Medical Society of London, May 1945.

he should. In any case we cannot dam the stream of research effort, even if we do see too much of it losing itself in the sands.

It is significant that it is in medicine, and not in its so-called ancillary sciences where the situation is not essentially different, that an acute consciousness of the dilemma I am considering should first have dawned. Reasons for this are easily found. Let us take the case of physiology as example. This is now busily exploiting the harvest of technological advances in all fields of science, and is adapting to the solution of its own problems the methods which these sciences—physics, chemistry, and biochemistry—are so richly providing.

It has thus come about that a given physiological problem, such as the nature of cerebral cortical function, may now be approached from so many angles that it assumes the appearances of, and is too readily taken to be, many disparate and unrelated problems. All effective communication in thought tends to be broken between the users of the different exploratory techniques, and information accumulates while generalization wilts and dies. To use an expression familiar to readers of war reports, the physiologists are "fanning out" into the unknown, and in this active stage of their advance fail adequately to realize that co-ordination of thought and aim must be retained if physiology is to be a coherent body of knowledge. Let me take again, as an example, the problem of localization of function in the cerebral cortex. Over fifty years ago Hughlings Jackson, the clinician who discovered the *fact* of localization of function within the cortex, being a man of ideas, also made some penetrating generalizations as to the *nature* of this localization. The era of experimental study of this problem opened very shortly afterwards, and has since been pursued with ingenuity, with eagerness, and by an increasing number and variety of techniques—the most modern ones being of great refinement and delicacy. Yet there has been no comparable development of thought upon the subject, and a crude notion that sees in the cerebral cortex a mosaic of sharply delimited localizations of fragments of function has survived virtually unaltered since the pioneer

experimental investigators first bent their energies to the task of discovery. During all this time Jackson's interpretation and synthesis of the facts have scarcely influenced thought. It is not that this interpretation has failed to generalize the facts, it is simply that it has largely failed to excite the interest of research workers. The taint of ideas that clung to it, and the bend sinister of its clinical pedigree, have together provided the experimentalist with an excuse not to think about it.

Nor is this preoccupation with the collection of information the only factor in the disorderly state of knowledge on this and allied subjects. As Trotter has pointed out, and abundantly exemplified, in more than one of his penetrating addresses, physiologists commonly, and naturally enough, pursue their science for its own sake. Theirs is therefore by definition a liberal profession, while that of a physician is a useful one. I make this distinction in no invidious sense, but in the sense employed by Newman in his lectures on "The Scope and Nature of University Education," where he says: "That alone is liberal knowledge which stands on its own pretensions, which is independent of sequel, expects no complement, refuses to be informed (as it is called) by any end, or absorbed into any art in order duly to present itself to our contemplation." This quality, which physiology as a branch of liberal knowledge shares with such physical pursuits as cricket and fox-hunting—as Newman also points out—is not shared by medicine, whose activities have an end other than themselves, namely, the health and well-being of the community.

I do not wish to be taken as implying that the fruits of physiological research are not useful—indeed, we know that they are not rarely potent weapons in our hands—but as emphasizing that this last result is, when it happens, fortuitous, and is not one that the physiologist as such intends or is interested in. In short, in medicine we have to apply our knowledge, however garnered, to well-defined ends, to the prevention and cure of illness and, as a corollary to this, to the training of the doctors of the future. It is this that brings home to us, whether we will or not, the dangers inherent in the unceasing expansion and differentiation of

the field of knowledge. As has been aptly said, once we seek to go beyond the basic elements of medicine as we know it, we tend to know more and more of less and less. Thus it happens that those responsible for the training of our successors too often find themselves imparting unrelated categories of information and partial and often conflicting generalizations culled from different fields of medicine, and it is becoming nobody's business, and seems less and less within anyone's capacity, to teach medicine as a whole, or to build into a coherent body of knowledge the several contributions of the specialists.

It is therefore because ours is a useful rather than a liberal profession that we have been forced to face the situation created by the accumulation around us of more, and more diverse, information than we can digest and assimilate. Hughlings Jackson was clearly aware of this, over fifty years ago, when he said that "we have multitudes of facts, but we require, as they accumulate, organizations of them into higher knowledge ; we require generalizations and working hypotheses. The man who puts two old facts into new and more realistic order deserves praise as certainly as does the man who discovers a new one. There is an originality of method." But in this, as in much else, Jackson was before *his own time and ours ; and thus it is that physiology*, true to its nature as a branch of liberal knowledge, sees no reason why it should not continue to browse at will upon the rich pastures of uncropped knowledge, giving no thought to any philosophy of knowledge, while medicine, faced by its ultimate purpose, has clamant responsibilities in the ordering of the knowledge at her disposal, and in the maintenance of a balance of activity and thought, that she dare not continue to evade. Medicine, then, has come to see that the unending additions to knowledge call urgently for a corresponding measure of integration. Yet we must try to strike a fair balance in this matter. Let it not be thought that I am making odious comparisons between physiologist and physician. We are both in the same boat, and in medicine we need not flatter ourselves that it is primarily out of any intellectual disquiet, or out of a divine discontent with the chaos of information that lies around us, that we have been

brought to realize our dilemma, namely, the necessity and the evil of specialization. We are as innocent of any philosophy of knowledge as the physiologist. Our concern arises because much that is implied in the term "specialism" has come to be an obstacle to the teaching and practice of medicine.

Nevertheless, by whatever channel this awareness of the disorderly state of our science has reached us, we are at least generally agreed that we cannot indefinitely go on as we are, and that something must be done to bind the broken foundations of medicine and to make it something more than a congeries of ingenious techniques and unrelated fragments of knowledge. This, at any rate, however gained, is something gained.

Integration keeps Pace with Differentiation

The thought that I am trying to develop will be familiar to many of you. It is summed up in the aphorism so familiar to neurophysiologists, "Integration keeps pace with differentiation." This is a fundamental principle in the evolution of the nervous system, and I cite it because I believe it to have a vital meaning for us in my present connection. We owe its original formulation to the now disregarded genius of Herbert Spencer, from whom it was taken and so fruitfully employed by Hughlings Jackson. Derived anew from this latter source, it became a guiding inspiration in Sherrington's monumental contributions to experimental physiology, and its influence may be seen in the title he gave to his classic work of 1906, "The Integrative Action of the Nervous System." Yet it is not so much with integrative action of the nervous system in respect of the organism as a whole that I am concerned as with the development within that system, as it becomes progressively more differentiated, of structures and functions designed to control and to unify the several parts and to make them into a harmonious whole. In short, integration does, as an observed fact, keep pace with differentiation in the evolution of that system.

This conception is capable of a wider meaning than that given to it by the physiologist. I submit that it expresses

something inherent in scientific thought and constantly found in truly scientific endeavour.

Let us now replace the term "differentiation" by "observation" and the term "integration" by "interpretation and synthesis." Observation leads to the increase and differentiation of information, while interpretation and synthesis are its integration into ordered knowledge, and I suggest that in the process of scientific thinking interpretation and synthesis must keep pace with observation if a coherent body of knowledge is to be forged. From this we pass easily and naturally to the notion that there is a rhythm in scientific thought, the two elements observation and interpretation alternating.

The feeling that there is such a natural rhythm in thought, a cycle in which observation and interpretation alternate, is widely implicit in our literature in respect of all branches of knowledge. It finds expression in such a statement as that of Lord Acton : "The main thing to learn is not the art of accumulating material, but the sublimer art of investigating it." While in Matthew Arnold's essay on "*The Function of Criticism*" we read : "The grand work of literary genius is a work of synthesis and exposition, not of analysis and discovery." Coming to our own field, we find Abraham Flexner writing : "Data of one kind or another are not so difficult to obtain ; but generalization is another matter. . . . The two processes—the making of hypotheses and the gathering of data—must go on together, reacting upon each other." But the notion gets its fullest and most explicit formulation in a passage from the first volume of Arnold Toynbee's "Study of History," which I have already quoted elsewhere, and do so again, to reinforce the cogency of my theme with the authority of this erudite thinker on history. He says :

> "Scholarship makes its progress by a rhythmic alternation between the two activities—the collection of materials and their arrangement, *the finding of facts and their interpretation*—just as a physical organism lives and grows by an alternation between eating and digestion. The old fable of the belly and the members points the moral that neither activity is superior or inferior, prior or posterior, primary or parasitic, but that each is inseparable from the other as a part of the

same whole, and complementary to the other as a phase in the same recurrent process. For the alternation perpetually recurs in virtue of the very nature of thought. When the mind is employed in finding facts, its sheer success inhibits it sooner or later from fact-finding uninterruptedly and *ad infinitum*. Sooner or later it finds itself so formidably beleagured by the mass of facts which it has gathered round it that, until it has sorted them out and arranged them in some kind of order, it can no longer sally out into the Universe to gather more. Then the mind changes its activity perforce and employs itself for a season in making syntheses and interpretations. Yet now, once again, its sheer success inhibits it from working uninterruptedly and *ad infinitum* at bringing order out of chaos. Sooner or later it finds that it has reduced to order all those materials which it had collected in its last fact-finding reconnaissance. Fresh facts must now be found before the process of synthesis and interpretation can be carried further. . . . No collection of facts is ever complete, and no synthesis or interpretation ever final. . . . This rhythm is native to thought in all its different channels. In the channel of Physical Science, we have seen that thought has recently passed out of a fact-finding phase into the next phase of synthesis and interpretation."

Thus Toynbee, and, *mutatis mutandis*, what he has to say of the study of history applies to medicine and the sciences ancillary thereto. In a remarkable foreword to his book on anaphylaxis and immunity, Maurice Arthus, with a true French clarity, tells us how this balance is to be achieved, and how vital to science it is. This foreword has recently been translated into English under the title of "The Philosophy of Scientific Investigation" by Sigerist, and published by the Johns Hopkins Press. He says :

> "The experimentalist must ponder and meditate deeply over the problems raised. . . . In order to make some progress in the experimental sciences one must meditate a great deal. I have repeatedly mentioned," he goes on, "the necessity of controlling the facts observed, of discussing the interpretations proposed and the meaning attributed to them, in order to accept as true and valid only what has stood the indispensable test of scientific criticism. This presupposes a special mental attitude which, unfortunately, is hardly developed in the schools, colleges, or perhaps even in the universities, namely, critical sense. This is the tendency of the mind to seek the true value of facts and results, of methods and of concepts."

It should not be necessary for me to labour this point any more, yet I believe that few would contend that during our time either medicine or its ancillary sciences have consistently honoured these principles of scientific thought, or have conformed to this rhythm of which Toynbee speaks as "native to thought in all its different channels." We have, in fact, with some brilliant exceptions, been far too readily satisfied with fact-finding, and two little regardful of those intellectual instruments by which facts are interpreted and generalized. The work of Hughlings Jackson was such an exception, and another that stands out in my mind is that of Sherrington in the field of physiology. I can yet recall the feeling of exaltation with which, as a student of physiology over thirty years ago, I first read his "Integrative Action." Here were new facts of observation in rich abundance, and how beautifully co-ordinated! With what logical precision the exposition of them advanced from step to step, and with what penetrating scientific imagination was their significance revealed! This perfect rhythm of observation, interpretation, and synthesis, which is the hall-mark of scientific genius, has characterized all Sherrington's work and has made of it a unified whole, a brilliant chapter in the story of the nervous system.

In the clinical field we see the same brilliant qualities informing the studies of Trotter and Davies on cutaneous sensibility. Here, within the brief scope of two papers, we find as complete a harmony of observation and interpretation and as finished a piece of medical research as modern medicine has to show. A comparable trend is seen in Head's work on sensation, a rhythm of observation and interpretation and a continuity of thought over a long-sustained research; and if the observations in some details have since proved fallacious and the interpretation sometimes unduly abstract, the whole is an impressive example of the normal rhythm of scientific thought with its own elements of grandeur.

To sum up this stage of my thesis, therefore. we see that as new facts increase in number and diversity, the need for their interpretation and synthesis increases in corresponding degree. By these means we forge those general principles that keep knowledge coherent, and make of it truly scientific knowledge.

One is sometimes asked what, precisely, one refers to by principles of medicine, and I admit that the term is apt to be used without due definition. Let me tax your patience by yet another example from the field of neurology. The generalizing mind of Hughlings Jackson, surveying the wide range of phenomena of disease of the nervous system, discerned that the totality of these phenomena could be subsumed under four headings, that the functions of the nervous system could react to damage in but four essentially different ways, whatever the nature of the pathological process concerned. He thus was able to formulate four corresponding generalizations. He then went further, and, taking the phenomena of nervous disease as a whole, he saw that these constituted an orderly reversal of the natural evolution of function in the nervous system, whether considered phylogenetically or ontogenetically. He was thereupon able to formulate a further and wider generalization —namely, a general principle of dissolution of function in the nervous system. Although seventy years have elapsed since this was expounded—years rich in new knowledge of relevance to the problem—it still provides a generalization of wide validity and great usefulness. Thus, however discouraging the therapist may find diseases of the nervous system, we have in neurology a coherent body of knowledge more closely based upon anatomy and physiology than any other branch of medicine, saving only cardiology, which has a body of general principles of a like order. Such a consummation should be our aim over the whole field of medicine.

No one will deny that there are dangers inherent in the use of generalizations—for example, the tendency to fit the new facts into the procrustean bed of theory, where knowledge may become rigid and die. Incautious abstract thinking has, indeed, been described as "a major vice of the intellect," and no one has spoken more cogently of its dangers than Trotter. Nevertheless, he has also told us that ideas keep science fresh and living, and when properly used are in no danger of ceasing to become the nimble servants of truth. Therefore, even though the intellectual instruments of abstract thought and generalization may turn in our hands, we must yet use them if we are to advance.

Now, those of you who may be ready to accept the point of view I am trying to advance may still ask me how we are to apply it. How are we to reduce the vast accumulation of facts to some sort of order, to elicit general principles, and to build a coherent science and art of medicine? From the very nature of things we shall never achieve finality, but at least we can try to tidy up as we go along.

I believe, in brief, that we must be imbued with a vivid realization of the fact that scientific thought and activity make up a rhythm of which observation on the one hand, and synthesis and interpretation on the other, are the elements, and that the mere eliciting and recording of factual details are by themselves not science, and do not become so until the cycle is complete. In other words, we need a wholesome respect for ideas as an integral part of scientific thought. I cannot help thinking that if in every centre of original work, clinical and laboratory, workers were constantly aware of *the principle that integration of knowledge should keep pace* with its differentiation, we should find many fewer disjointed and apparently purposeless observations swelling the monstrous bulk of scientific literature. I sometimes doubt whether one is justified in recording in print a new observation unless one also seeks to indicate what it holds, and to apply the inductive process to it. One should not fling a raw fact on to paper in public, as a keeper flings a chunk of raw meat to a tiger. I believe that in medicine we have a unique advantage in this respect over the purely experimental scientist, in that medicine, while becoming increasingly an experimental, has long been and must continue largely to be an observational science. In its observational aspect it deals with a supremely difficult material under conditions that make constant demands upon intuition and judgment. Nature is not interested in scientific method, and the experiments she provides for us in the guise of disease and injury we have to take as we find them; *we cannot subject them to the necessary but artificial* simplification that is the essence of a good experiment. *We are therefore forced to think, to synthesize, and to* interpret our evidence to a point rarely necessary in the designed laboratory experiment. While, therefore, we must

welcome the increasing rôle of experiment in the study of medicine, we must be on our guard not to be infected by the distrust of ideas characteristic of much experimental work, but continue to use the intellectual assets which experience of clinical observation gives every good doctor.

I confess that I have inflicted many quotations upon you, a fault which one filling the rôle of orator should never commit, but my object in doing so is to emphasize, as clearly as I am able, that my thesis is no new one, no private bee buzzing in my bonnet, but one that has often been maintained and exemplified by those whose labours in the realms of observation and ideas have shone most brightly before us.

Tasks Involved in Rebuilding of Medicine

If you have followed me so far, you will probably agree *that there is one simple way in which each of us can contribute to the integration of medicine*—by seeing that in any addition we may be able to make to the sum of medical knowledge we tidy up as we go along and conform to the natural rhythm of scientific thought, and that we try to build our fragmentary contribution into the general body of relevant knowledge.

A second task involved in the rebuilding of medicine is to ensure, as and when the human resources are available, *that those who hold key positions in centres of medical* education and research shall be men interested not only in research and routine teaching but also in general ideas.

This may prove no easy task, for such men are rare, and the trend of values hitherto has not been such as to encourage them to follow their bent. You cannot find them by offering professorships, as some suppose, but you can always offer them full opportunities when you find the men. Encouragement must begin when they are young, and before they become moulded or resigned to the ephemeral patterns of current orthodoxy. The young worker must be allowed to retain his intellectual independence and to pursue the problems he has found for himself—as the best men do find them for themselves ; he must also be allowed some vestige of freedom by the editors of those scientific journals

in which his work reaches the world, in developing his ideas, so that his papers are not reduced by the editorial blue pencil to those drab sequences of experimental protocols that for too many appear the ideal of a *scientific paper*. *An editor* should be " no envious Juno sitting cross-legged over the nativity of any man's intellectual offspring," as Milton says; and whoever believes that the censorship of ideas survives to-day only in the totalitarian State imagines a vain thing. The original sanctions may have gone and a censorship's formal existence have ceased, but the itch to suffocate the infant idea burns in us all in greater or less measure.

I may seem to have wandered far from my opening theme, namely, the evil and the necessity of specialism in medicine, but I believe that, in fact, I have not done so. The danger of specialism is not so much that a man devotes his major activity to a restricted field of knowledge in medicine, but that he is so apt to become absorbed in its details, and still more in those of the complex instruments that are now so freely at his disposal, that he unwittingly cuts adrift from the general body of medicine and goes off on a voyage of his own.

There are in truth no irrelevances and no contradictions in nature, nor can there be in any coherent body of knowledge. The specialist, therefore—and I use the term *in its strict and not in its journalistic sense—must cling fast* to the foundations of medicine, for only thus can he integrate his contributions to knowledge and orient them, and avoid the multiplication of those conflicting *ad hoc* hypotheses with which medical and allied literature are littered.

So, too, the teacher of medicine has a like obligation to interpret as far as possible and to keep a lively interest in general ideas. This applies with greater force to the academic than to the purely clinical teacher, who has a major responsibility in handing on the art and the techniques of medicine.

Last, there are our textbooks. It has now become the almost universal practice for a textbook of medicine to be the algebraical sum, if not often the integration, of the knowledge of a body of specialists. There is a danger inherent in this plan, forced upon us though it may be, for

it demands in the editor of such a compilation gifts of detailed knowledge and of generalization that few can hope to possess. In these circumstances, also, an editor has to have a clear idea as to the circle of readers he is providing for, as to the particular want he desires to satisfy. What is best for the student is not necessarily adequate for the follower of higher studies, and what the latter requires is not the diet for the student. Too often we see an attempt made to make the best of both worlds, with the result that neither is wisely catered for. Of all textbooks it may not unfairly be said in our day that they are more interested in facts than in ideas, and an urgent task before us is some recasting of them. It is significant of the trend of current thought that whereas formerly textbooks of medicine claimed to expound the "principles and practice" of medicine, no modern work of the kind makes even a titular claim to concern itself with principles.

Finally, there is a pseudo-integration of medicine against which we are not always sufficiently on our guard. This is *exemplified in the numerous doctrines of those who see their* own specialty everywhere in medicine, who have their own touchstone by which all the phenomena of illness are to be assessed. They measure every man's corn by their own bushel, and are obsessed by this or that cult of ideas and are always proselytizing. They make up those cohorts of hobby-horse riders who cavort noisily to and fro across the field of medicine, throwing up dust into our eyes.

The Rôle of General Education

Now if this notion of what is requisite to advance in medicine has validity it must presuppose an adequate general education as a foundation. If those who come after us are to be equipped to observe and describe accurately and interpret logically and imaginatively, their training to these ends must begin while they are still young, and their school education should not be based upon short-sighted utilitarian considerations, or be of what I may call a polytechnic order, but should include as its very foundation a thorough training in the use of that noble instrument for the expression of

thought and feeling, our mother tongue, in the expansion of that *instrument by the right use of analogy, and in its* logical employment.

In brief, what I am invoking are the three arts of grammar, rhetoric and logic. If we lack a command of language we cannot hope to produce, formulate or entertain general ideas or make even the simplest essays in abstract thinking.

Now, those who are familiar with the aims and methods of the mediæval university will recall that these three arts, composing what was called the trivium, formed the basis of university education. It may perhaps be argued that in the Middle Ages, the ages of scholastic philosophy and of theological disputation, these three arts tended to be followed *as an end in themselves, that the training in clear exposition* and thought was what I have already called a liberal education with no end other than itself, and that it led to mere logic-chopping and to no advance in natural knowledge. Some of this may be true ; I express no view upon it, and I am not proposing the revival of these arts merely as an entertaining and stimulating variety of mental gymnastics. I put them before you as an essential preliminary to that clarity of thought and expression that is one of the weapons of scientific advance, of the tools with *which we pursue natural knowledge. From this it* follows that the greater our command of language, the more clearly and deeply we can think and express our ideas. I submit, therefore, that a command of language, and its logical use, are vital preliminaries to any scientific training.

Some may ask me where rhetoric comes in. In its original and its mediæval sense it refers to the expansion and condensation of discourse by analogy and figure of speech. Wherever we find lucid and vital English, there we find rhetoric. What a text of lovely and *illuminating rhetoric* are the psalms, for example. Rhetoric has its place in the expression of those ideas we derive from the study of facts, *nor can we teach without it.*

In short, what I am proposing is that a humane education is an invaluable asset to any youth embarking upon the

study of medicine. I am aware that I raise the banner of a forsaken cause when I say this ; but, nevertheless, twenty-five years of clinical teaching have fully persuaded me that when I find a clinical clerk who can stand up and read at a ward visit a case history that is a well-ordered, lucid, and fluently expressed account of the patient and his situation, that student will almost invariably be found to have had a sound education, and not a mere course of instruction of the polytechnic order, a utility education. This is why we must all deplore the practice of turning boys over to premedical subjects exclusively, or almost exclusively, directly they jump the hurdle of the school certificate. Too often they come to us semi-articulate, their budding ideas imprisoned behind the bars of an inadequate command of expression. It is between the ages of fourteen and eighteen that the capacity for pursuing a line of thought and for abstract thinking develops, and it is then that the adolescent should find himself provided with the necessary instruments of speech. " Give me," says Milton, " the liberty to know, to utter, and to argue freely." If we changed this by saying " Give me the literacy to know, to utter, and to argue freely " we should not really be altering the sense, for it is the capacity to express it that gives liberty to thought.

Conclusion

What I have had to say is somewhat remote from the medicine that presents itself to us in our daily lives. Yet as we grow older the urge to lift our eyes from the details of the little plot in which each of us labours becomes ever stronger, and we are impelled to look round upon the wider field of natural knowledge as a whole. Some may even feel the pull towards some philosophy of knowledge, towards those common truths to which all science must be obedient. Man does not live by facts alone, but craves also for generalizations, and the desire for some philosophy of knowledge burns, if with varying intensity, in all of us.

Looked at in this spirit, how untidy and in places how overgrown the field of medicine seems to be ; in other places how bare, how precariously balanced the whole

upon the uncertain foundations of biological knowledge! So it must remain until we develop a wider and deeper consciousness of what constitutes ordered knowledge and of the cycle of thought by which it is to be achieved.

Yet, to feel some discontent with medicine as we find it does not imply any lack of pride in its achievements, nor any diminished sense of privilege in seeking to serve it. If one is a critic, it is, I trust, in the spirit expressed by Milton when he says: "For he who freely magnifies what hath been nobly done, and fears not to declare as freely what might be done better, gives ye the best covenant of his fidelity."

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